THE American Journal OF Gastroenterology

VOL. 30, NO. 1 JULY, 1958

Stricture of the Bile Ducts

Medical Problems in Biliary Tract Disease

Surgical Problems in Biliary Tract Disease

Hematologic Changes in Chronic Liver Disease

Management of Hepatic Coma

The Impact of Antibiotics on the Gastrointestinal Tract

Twenty-third Annual Convention
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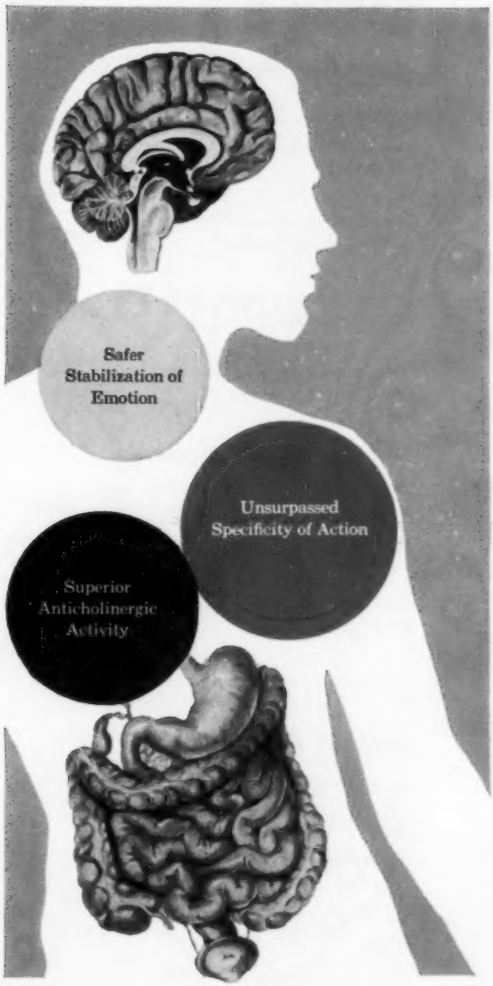

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The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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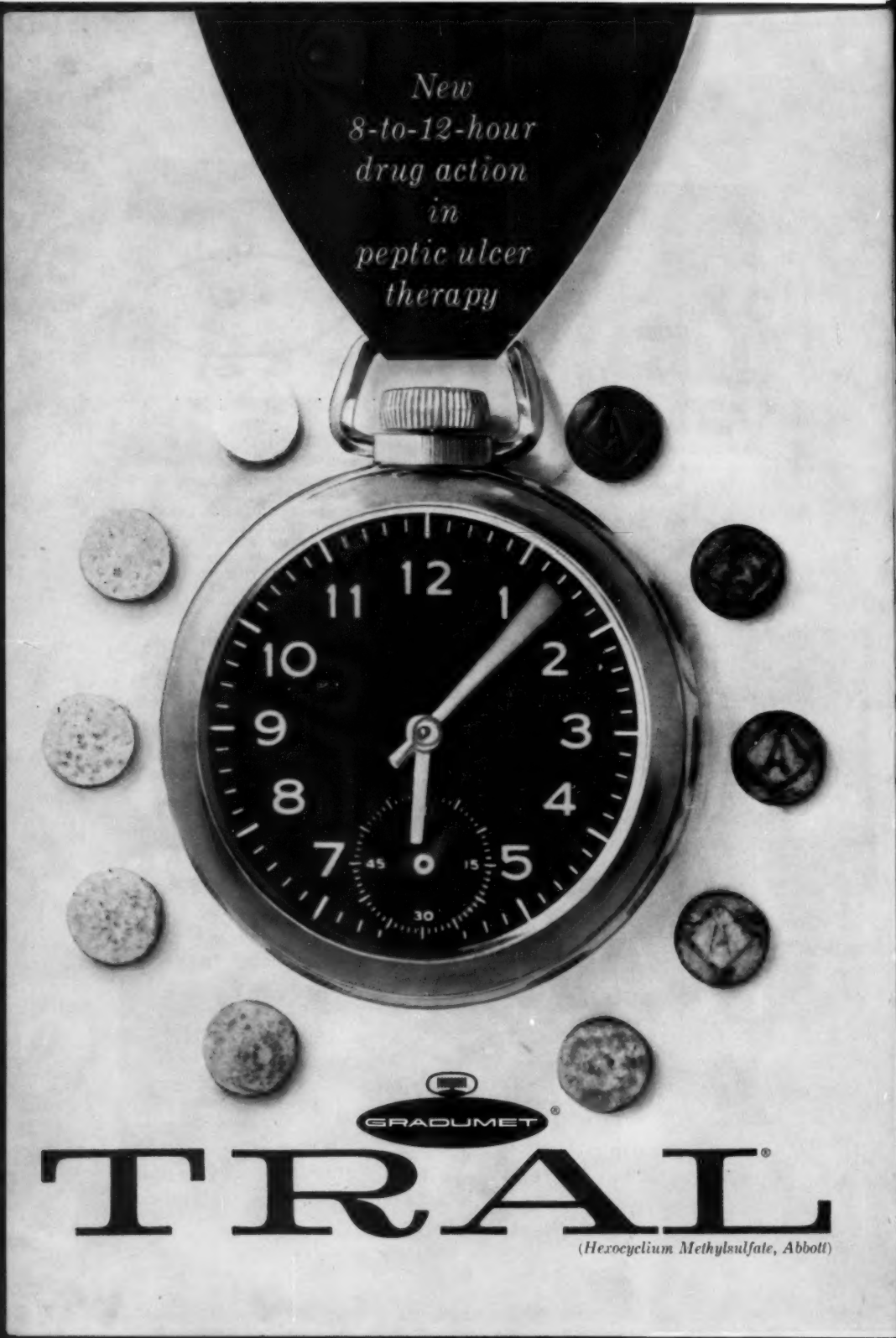
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STRICTURE OF THE BILE DUCTS*

DONALD E. ROSS, M.D., F.A.C.S., F.A.C.G.
Los Angeles, Calif.

The literature is replete with articles written by master surgeons on the subject of bile duct strictures. Despite all the warnings contained therein, trauma remains the principal etiological factor. It seems necessary, therefore, to discuss the subject again and renew the instructions for the prevention of operative injury. The part played by inflammatory reactions in the production of strictures is emphasized. It is also urged that primary cancer can, in many cases, be surgically removed with some hope of cure or reasonable palliation. A new technic of anastomosis which enables the surgeon to more easily obtain accurate mucosa-to-mucosa union will be described.

The major etiological factors in strictures may be classified as follows:

1. Congenital atresia
2. Traumatic
3. Inflammatory
4. Carcinoma of the bile ducts

CONGENITAL ATRESIA

It must be emphasized that these cases are not all hopeless. Hicken states that at least 24 per cent may be operated with a fair chance of cure. A careful search of the operative field may reveal a duct or gallbladder which may be rudimentary. When this is filled with radiopaque media an x-ray may be taken and this helps to visualize the entire duct system. Saline injected into the ducts distends them so they are outlined to better advantage and, in addition, facilitates anastomosis. It may then be possible to anastomose the gallbladder or a distended duct to the duodenum or jejunum. Atresia may involve the intrahepatic ducts as well as the extrahepatic ducts. In such cases there is very little

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Boston, Mass., 24, 25, 26 October 1957.

hope of definitive surgery. The Longmire operation has been tried but has not been successful in this type of case since the bile ducts are too small for anastomosis and often there is not an adequate collateral connection with the right lobe. Longmire removes the left lobe of the liver and hopes to find a bile duct large enough for anastomosis. It is important to remember that a diagnosis from icterus neonatorum and other conditions necessitates waiting at least one month before surgery is attempted. An example of successful surgery in this type of case is reported.

Case 1:—H. H., male, age 21 years, gave a history of having been operated upon by Dr. W. E. Ladd of Boston at the age of nine weeks. At that time he had been jaundiced for four weeks previous to surgery. An area of atresia was present in the common bile duct just proximal to the duodenum. An anastomosis between the common duct and the duodenum was accomplished.

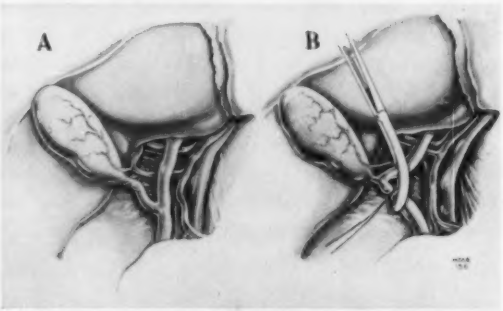

Fig. 1—A. The right hepatic artery is seen passing behind the common hepatic duct. The cystic artery in this case is very short. The right hepatic artery could be ligated on the erroneous assumption that it is the cystic artery. This might cause the death of the patient.
B. Illustrates operative errors which are still occurring. 1. The common duct is seen to be ligated on the presumption that it is the cystic duct. 2. The hemostat is shown clamping off the common hepatic duct and the common bile duct on the supposition that one is or both are the cystic duct.

The patient enjoyed good health until recently when a gradual onset of jaundice occurred. On 8 June 1956, he was reoperated upon by Dr. James Regan. The findings at this time were a diseased gallbladder and a stricture of the common bile duct at its junction with the duodenum. Situated just above the stricture in the duct was a gallstone about 1 cm. in diameter. A cholecystectomy was performed. The common duct was then divided immediately above the duodenum and the gallstone removed from its lumen. A new anastomosis between the common bile duct and duodenum was carried out, using the technic suggested by the author and illustrated in Figure 8. This method enables the surgeon to obtain mucosa-to-mucosa suturing which is important in this type of surgery.

Traumatic Stricture

Cole estimates that 80 per cent of strictures occurring in the bile ducts are caused by operative trauma. Cattell's estimate of 90 per cent is even more alarming. To avoid "getting into trouble" the surgeon should remember that anomalies of the ducts and blood vessels frequently occur. Cole states that in 15 per cent of cases there are accessory cystic ducts. The occurrence of accessory ducts from the liver frequently are present. In 16 per cent of cases, the cystic artery crosses over in front of the duct. In 16 per cent, the right hepatic artery is anterior to the duct. In 20 per cent, the right hepatic artery runs parallel to the cystic duct and in this case, the cystic artery is often very short

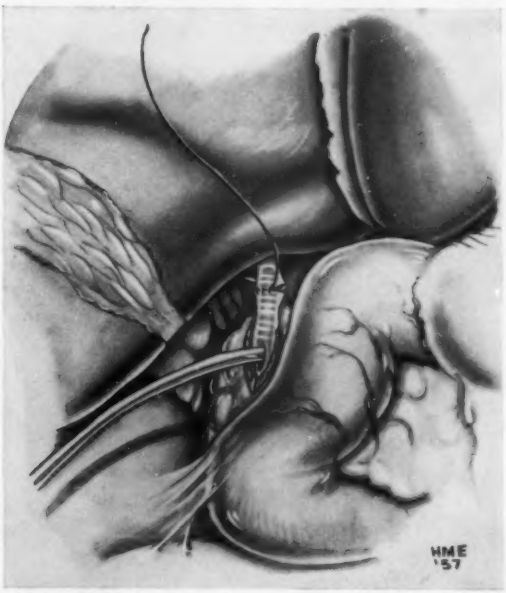

Fig. 2—The duodenum has been mobilized to allow approximation of the ends of the bile duct. The pancreas has been separated over the bile duct. Through this portion a T-tube has been inserted.

(Fig. 1). It would be very easy to tie off the right hepatic artery believing it to be the cystic artery. When this calamity occurs, death within a few days will follow in at least 50 per cent of these patients.

To avoid damage to these structures it is necessary to employ a large incision, obtain good relaxation and have adequate exposure and good light. Before division of any structure, it is most important to have the common duct, the hepatic duct and the cystic duct well exposed and identified. It is also important to identify the foramen of Winslow. Should hemorrhage be encoun-

tered it may readily be controlled by placing a finger in the foramen of Winslow and compressing the hepatic artery between the finger and the thumb. The bleeding site may then be identified, picked up and ligated. Clamping blindly through a pool of blood must never be done as this assuredly will damage the duct which later may cicatrize and cause a stricture. The cystic artery should be dissected and ligated before division of the cystic duct, otherwise, undue tension may be exerted on the artery resulting in tearing and hemorrhage.

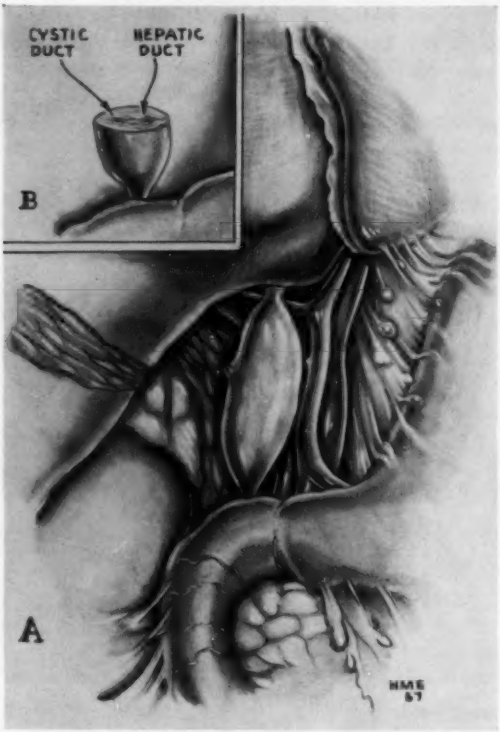

Fig. 3—A. Inflammatory rusiform swelling or tumor of the common bile ducts is illustrated. B. A cross section of the inflammatory swelling shows two small ducts. One of these is the common bile duct and the other a "low-lying" cystic duct. Both ducts are very small and are surrounded by a mass of dense fibrous tissue.

Probably the most common cause of injury to the ducts results from pulling them up at an angle which may be called "tenting" (Fig. 1). Under these circumstances, the common bile duct may be clamped and ligated on the assumption that it is the cystic duct, or even a section of the bile duct may be removed with the gallbladder. If there is poor exposure, dense adhesions, edema or other difficulties, the surgeon should not hesitate to remove the gallbladder from

above downward. In any case, there is no place for haste when performing a cholecystectomy but conversely, careful and deliberate dissection will keep the surgeon out of danger.

One objection raised to the indiscriminate exploration of the common duct and drainage with a T-tube is the danger of stricture at the point where the

Fig. 4—A primary cancer of the common hepatic duct (Case 6) is illustrated. The right hepatic artery is seen passing behind the fusiform enlargement of the common hepatic duct. The right portal vein is posterior to the right hepatic artery. When these structures are retracted backward, it is safe to resect tissue from the hilus of the liver.

duct was opened and drained. This does not seem to be an important etiological factor since the author has not seen such a complication.

Bakes' graduated probes are usually used to explore and dilate the ampulla. If larger than 7 mm. dilators are used, the sphincter area may be traumatized with subsequent fibrosis and stricture formation.

The presence of a stone which has remained for a considerable time at the same spot in the duct may traumatize the duct with resultant scarring.

An example of trauma occurring during surgery is illustrated in Case 2.

Case 2:—Mrs. V. L., age 45 years. On 2 November 1954 this woman suffered from jaundice and gallstones for which a cholecystectomy was performed "elsewhere". Bile drained for three months and a subphrenic abscess developed which required reoperation and drainage. The patient continued to feel somewhat ill and the jaundice never entirely cleared. For the past three months the stools have been clay colored and jaundice has become intensified. The patient was operated by us 12 August 1956, and the findings were as follows:

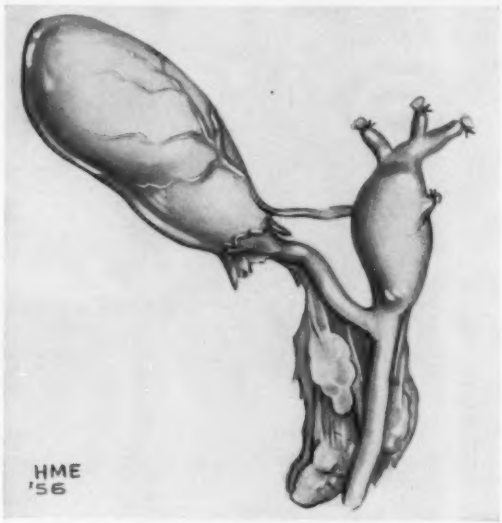

Fig. 5—The illustration shows the tissues which were resected. These include the gallbladder, the cystic duct and the common hepatic duct. The tumor had invaded the portal vein. The three prongs above this represent three hepatic ducts. In addition, the common duct, together with areolar tissue and lymph nodes in this area, were removed in continuity (Case 6).

The common hepatic duct was only 1 cm. long at the hilus of the liver. There was another stump of the bile duct extending up from the pancreas and duodenum about 2 cm. The intervening portions of the bile ducts were absent. By mobilizing the pancreas and the duodenum it was possible to bring the two ends of the duct by dissecting a portion of the lower end from its pancreatic covering. The object was to bring the T-tube out through this portion of the duct (Fig. 2). The duodenum was brought up close to the hilus of the liver so that the two segments of the bile duct could be anastomosed end-to-end.

The patient made a good recovery, the jaundice clearing rapidly. The T-tube has been left in place and there has been no escape of bile around the tube. Bile empties readily into the duodenum. Digestion is good and the patient is gaining weight and feeling fine. It is our intention to leave the tube in place as long as possible.

Fig. 6–This illustrates the surgical field after removal of the tumor mass. Three holes are seen in the liver bed representing the open mouths of the intrahepatic bile ducts. The sutured area of the portal vein is where the wall had been invaded by the tumor (For further details see test, Case 6).

When a duct has been inadvertently severed during surgery, no harm is occasioned if the error is recognized and immediate end-to-end suture is performed using a T-tube which is brought out through another opening in the duct lower down. If the misadventure is not noticed at the time of surgery,

bile will continue to flow from the wound. In some instances, the flow of bile will cease and jaundice will appear. In other cases bile will accumulate in the peritoneal cavity and cause bile peritonitis. If it is decided that the duct has been severed, early intervention during the first 3 to 5 days is advantageous. Bile is a very irritating substance and causes local inflammation and edema.

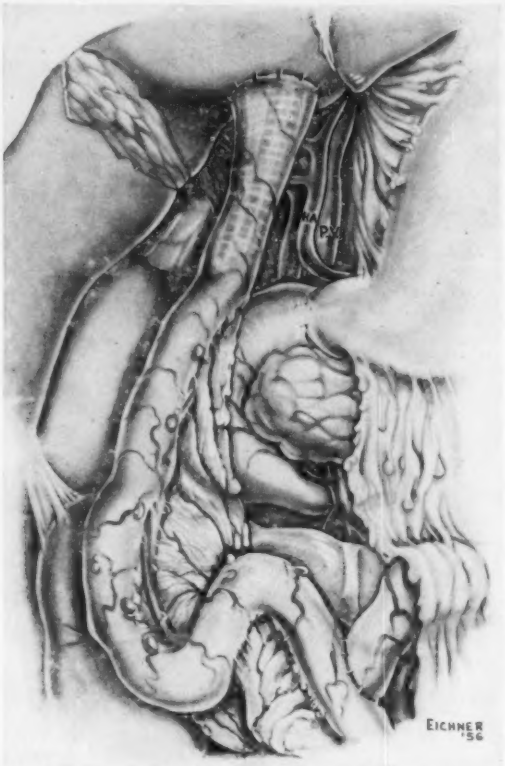

Fig. 7—This demonstrates the use of a loop of jejunum brought up by the Roux-Y method. In this instance (Case 6), the serosa of the bowel was carefully sutured all the way around to Glisson's capsule. The artist has attempted to show the polyethylene tubes hanging down into the lumen of the bowel (For details see text).

If intervention is not accomplished early, surgery becomes so difficult due to the macerated condition of the tissues that it is better to postpone the operation for 5 or 6 weeks.

Inflammatory Causes

Carter has suggested that an ulcerative cholangitis may occur and produce fibrosis and stricture formation entirely apart from any surgery. We have found

this to be true in many cases, not only during acute cholecystitis but, in chronic cases as well. It is therefore recommended that "silent stones" and those gallbladders which "fail to fill" during x-ray study should be operated without delay. When operation is performed during an acute cholecystitic phase, it is usual to find the acute edematous swelling has spread from the gallbladder to involve the full extent of the exposed bile ducts. Following such an inflammation, there may be serious fibrosis in the wall of the ducts. This process may lead to a narrowing of the lumen and even stricture formation. Sometimes partitions occur across the lumen causing a partial or complete obstruction to the flow of bile. Examples of this clinical entity are given in the Cases 3, 4 and 5.

Case 3:—F. H., male, 45 years of age. Ten years ago this man suffered an acute attack of cholecystitis and was operated "elsewhere". A cholecystostomy

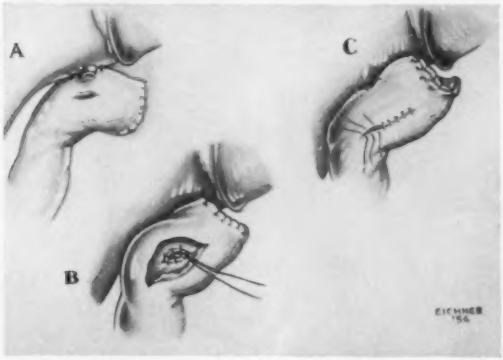

Fig. 8—A. A "button" has been removed from the bowel and the serosa has been sutured posterior to the bile duct.
B. The bowel has been rotated and another incision made in the intestinal wall which constitutes a "window" through which mucosa-to-mucosa anastomosis of the bile duct to the intestinal wall may be accomplished.
C. The anastomosis is now completed by additional serous sutures and enclosure of the "window" incision.

was performed. During the past 10 years, the patient suffered recurrent attacks of cholecystitis but the symptoms were never of such severity that operation was considered necessary by his doctors.

He was admitted to the hospital on 1 July 1953. The history at that time was recurrent attacks of fever and chills accompanied by slight jaundice. On 7 July 1953, he was operated upon. A cholecystectomy was performed during which it was noted that the bile ducts were exceedingly small. The first portion of common hepatic duct was normal for about 1 cm. in length and was dilated to about 1 cm. in diameter. The remaining portions of the common hepatic duct and the common bile duct were very small, and did not exceed 1 mm. in diameter. The bile ducts had suffered from atresia due to recurrent attacks of

inflammation which had presumably emanated from a chronically infected gallbladder. A piece of jejunum was brought up by the Roux-Y method. An end-to-end anastomosis was made between the jejunum and the short, normal piece of common hepatic duct. The bowel was opened about 3 cm. away and a rubber tube was passed through the anastomosis and then brought out through the intestinal wall by the Witzel method and then through a stab wound in the abdominal wall. The tube was left in place and drained bile for a period of four months at which time sedimentation appeared, requiring its removal. The

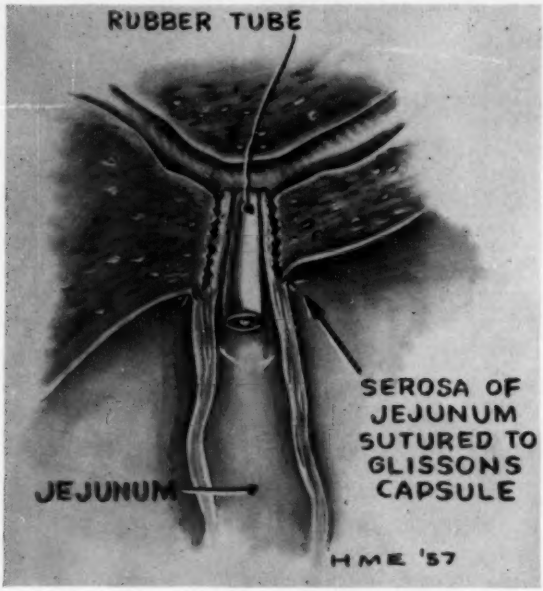

Fig. 9—In this case, no duct was available for formal anastomosis. A needle was inserted into the hilus of the liver and when the bile was obtained, a fusiform wedge of liver tissue was removed around the needle down to the dilated intrahepatic bile duct. A tube of mucosa is fashioned around a rubber tube and inserted into the hilus of the liver down into the dilated bile duct. The above method was originated by Warren Cole.

patient made a good recovery and there have been no complications or untoward symptoms after an elapse of four years.

Case 4:—Mr. O. R., age 65 years, was operated upon by us in 1955. At that time a cholecystectomy was performed. The gallbladder was thick-walled and contained several large calculi. At this operation, the bile ducts were not enlarged and were not explored. He was readmitted to the hospital on 25 March 1956, complaining of vague pain and a gradually increasing jaundice of three weeks' duration. The working diagnosis was probably stone in the common bile

duct. At operation, however, a fusiform thickening of the bile duct was found extending from the hilus of the liver to the point where the common bile duct disappeared into the substance of the pancreas. The greatest diameter of the thickened fusiform mass was 3 cm. (Fig. 3). The duct's wall was quite firm and malignancy was suspected. Certainly, the function of the duct had been destroyed. The proximal 1 cm. of the common hepatic duct was the only part which appeared normal. The spindle-shaped mass which constituted the thickened and obstructed ducts was, therefore, resected. The only available duct which was suitable for anastomosis was the stump of the hepatic duct at the hilus of the liver. Reconstruction was accomplished by bringing a loop of jejunum up by the Roux-Y method and anastomosing it to the stump of the hepatic duct.

The pathological report stated that when the fusiform mass was cut across a double lumen was encountered. These represented a common bile duct and a low-lying cystic duct. The duct lumen were very small in each case and it was evident that they could no longer function adequately. They were completely surrounded by dense fibrous tissue. The mucous membrane in these ducts was normal and there was no evidence of malignancy.

The entire thickening can only be explained as a chronic inflammation that persisted after cholecystectomy. The site of the continuing inflammation undoubtedly was in a "low-lying" cystic duct. From this focus inflammation spread to the remaining portions of the common hepatic duct and the common bile duct causing inflammatory swelling, fibrosis and atresia. The late bad results from leaving a long section of cystic duct is well known. A new gallbladder may develop. In one such case, operated elsewhere and reoperated by us, the gallbladder measured 9 cm. in length and contained stones. We have never, however, previously seen a case where the severe reaction affected that portion of the cystic duct which is intimately associated with the common duct as a "low-lying cystic" duct.

The patient made an uneventful recovery. The jaundice disappeared rapidly and the outflow of bile was satisfactory. After three months the tube was removed and since that time the patient has enjoyed excellent health.

Case 5:—J. C., male, age 44 years. A history of recurrent indigestion for about two years was obtained. The present attack was more severe and jaundice ensued which had been present for three days before he was admitted to the Queen of Angels Hospital. At operation on 17 August 1953, the gallbladder was acutely inflamed and was mottled with areas which varied from brown to green. The same discolored mottled and edematous condition which involved the gallbladder had also affected the ducts. A cholecystectomy was performed and since jaundice was present, an exploration of the bile ducts was carried out. The common bile duct was 2 cm. in diameter and was somewhat firm. When this was incised the wall was seen to be thick and fibrous and the lumen sur-

prisingly small. It was impossible to pass probes up or down the ducts because of partitions which had occurred across the lumen. A filiform bougie was used and threaded with difficulty down into the duodenum. Following this, a piece of ureteric catheter was used and then graduated metal probes. Dilation was continued up and down the duct until it was possible to insert a size 14 T-tube. A cholangiogram was made on the 21st postoperative day which revealed the bile ducts to be patent and the dye substance entered the duodenum without difficulty. The T-tube was inadvertently removed at this time. It had been my intention to maintain this tube in position for a long period. Despite its early removal the patient made an excellent recovery and continues to have perfect health without any symptoms since his operation which was four years ago.

Carcinoma of the Bile Duct

Primary malignancy occurring in the bile ducts usually involves the common hepatic duct. With increased experience the surgeon has become bolder in attacking this pathological condition. It is now realized that the only possibility of assisting the patient is to excise the carcinoma even though it requires courage and advanced technical skill. Because of the proximity of the carcinomatous mass to the liver, it has usually been considered inoperable. It will be demonstrated in the ensuing case report that when the components of the hepatoduodenal ligaments are carefully dissected, what seemed to be inoperable is, in reality, resectable.

Case 6:—E. L. C., male, 52 years of age, who suffered from slight jaundice and had dark urine. The date of admittance was 28 January 1956. The jaundice deepened and itching of the skin became intense. There was a loss of 8 to 10 pounds in weight during the two weeks before admission to the hospital. There was no pain at any time. The liver function tests indicated obstructive jaundice.

On 6 February 1956, a laparotomy was performed.

A right subcostal incision was made. A fusiform firm mass was noted involving the entire common hepatic duct and extending down to the cystic duct (Fig. 4). The swelling of the common hepatic duct measured 3 cm. at its greatest diameter. The tumor extended into the hilus of the liver and only by careful dissection in this area was it determined that resection was possible. The lymph node, which is commonly seen along the common duct, was firm. A diagnosis of carcinoma could be made with reasonable certainty. It was decided to remove the tumor as widely as possible. The gallbladder was, therefore, removed together with the common bile duct which was severed just above the pancreas. The portal vein was seen to be invaded in one location by the tumor. A small Satinsky clamp was used to close off a portion of the portal vein while the affected area of the wall was removed. Repair of the portal vein with fine silk sutures was not difficult. It was expedient to carefully dissect and separate the components of the hepatic ligament. When this was done, the right hepatic artery was seen to pass behind the common hepatic duct. It was also noted that

it could be separated from the areolar tissue in the hilus of the liver so that it could be retracted posteriorly. This retraction made it possible to remove a cone of hilar tissue in continuity with the tumor mass and to sever the hepatic ducts at some distance from the malignancy. When this had been accomplished, three large hepatic ducts were seen emptying into the common hepatic duct. These three ducts were divided about 1 cm. above the tumor mass. The pathological specimen is illustrated in Figure 5. It may be noted that all the tissues removed were kept in continuity. Obviously these ducts were cut off so high that it was impossible to do formal anastomosis to the ducts (Fig. 6). A snug polyethylene tube was, however, threaded into each of these three bile duct radicals and was held in place by silk suture. After the removal of the bile ducts, together with the gallbladder and lymph nodes, a loop of jejunum was again brought up by the Roux-Y method and the open end of the bowel was sutured around the hilus of the liver, the serosa being carefully sutured to Glisson's capsule (Fig. 7). The polyethylene tubes about 10 cm. in length were allowed to hang down into the lumen of the bowel before the latter was sutured to the hilus of the liver.

The pathological specimen, when cut across, showed a markedly thickened, firm wall, the lumen was extremely small. Microscopic examination of the resected specimen revealed adenocarcinoma of the common hepatic duct. The mucous membrane showed ulceration. The cancer cells extended deeply into the thickened walls. None of the lymph nodes removed contained metastases and there was no evidence of any distant metastases.

The patient made an excellent recovery. The jaundice faded rapidly. The patient was discharged from the hospital on the 17th postoperative day. There is no evidence of any recurrence although two years have now elapsed.

Comment

When the surgeon is confronted with malignancy, heroic methods for its removal are justifiable. Otherwise, the patient is doomed.

When the bile ducts are accidentally severed, the best results are obtained by immediately anastomosing end-to-end.

When a localized stricture is encountered, a small section of the duct may be removed and the ends approximated and sutured end-to-end.

A T-tube is used and it should always be brought out at another point in the duct and not through the anastomosis.

If a larger segment of the bile duct is absent, approximation may be possible after mobilizing the duodenum and pancreas as suggested by Lahey and Cattell.

Tubes of various kinds have been used to assist in the anastomosis or to bridge a short gap. For the most part, these tubes consisted of rubber. Lahey,

however, used tubes of "bouncing clay" and Pearse suggested the vitallium tubes. This type of technic met with a high percentage of failure. When a fistulous tract has been used to carry the bile into the stomach or intestinal tract, failure has been almost 100 per cent.

When the ducts are all absent with the exception of a small segment of hepatic duct at the hilus of the liver, the best method is undoubtedly to use a loop of intestine, by the Roux-Y method, for anastomosis. Such procedures in the past have had at least a 25 per cent failure or recurrence rate due to a failure to obtain perfect mucosa-to-mucosa anastomosis.

The principle reasons for failure of anastomosis to the intestinal tract is that bile is an exceedingly irritative substance and produces chemical inflammation with subsequent scarring and obstruction. It is now definitely understood that unless accurate mucosa-to-mucosa suturing is performed there is danger of fibrosis and stricture formation. The most modern method of supplying a tube is to use a loop of jejunum by the Roux-Y method and suturing the open end of the intestine to the short hepatic duct at the hilus of the liver. An attempt is always made to unite mucosa-to-mucosa but this is often technically difficult to accomplish.

The author's new method of accomplishing mucosa-to-mucosa anastomosis has been found useful in obtaining this objective. This is illustrated in Figure 8a. The bowel is shown with serosal sutures having been placed behind and on either side of the hepatic duct. This unites the serosa of the bowel to Glisson's capsule. In addition, a small opening has been made in the intestinal wall and a "button" of mucosa has been removed. Figure 8b shows the bowel to be rotated and an incision has been made into the intestine on the opposite side. This incision constitutes a "window" through which the surgeon can perform the mucosa-to-mucosa suturing after the stump of the hepatic duct has been brought through the small "button hole" in the opposite side of the intestine. When the anastomosis has been accomplished, the "window" incision in the intestinal wall is closed (Fig. 8c).

The most difficult problem confronting the surgeon is where the ducts have been so completely destroyed that no hepatic duct is visible in the hilus of the liver. In this case, it has been recommended that a needle be used in probing the liver at the hilus. When a gush of bile is obtained the needle is left in place while a cone-shaped wedge of hilar tissue is removed down to the duct. Cole has devised a method by which a tube of bowel mucosa is fashioned over a piece of rubber tubing at the end of the intestinal loop. This is inserted into the excavated hilus of the liver and into the dilated intrahepatic duct (Fig. 9).

Where the above method is not feasible, the Longmire operation may be used. The principle is to remove a portion of the left lobe of the liver hoping

to find a large enough intrahepatic bile duct for anastomosis to a loop of intestine by the Roux-Y method.

Conclusions

It is hoped that constantly repeated warnings may have a salutary effect in reducing the number of operative injuries of the bile ducts.

Pediatricians are urged to be ever mindful of congenital atresia when considering the differential diagnosis of jaundiced infants. It is found that at least 25 per cent of these can be successfully operated.

Emphasis is now placed on the role which chemical inflammation plays in the production of acute and chronic cholecystitis. It is important to realize that this inflammatory process may, and often does, extend onto the bile ducts and may involve them in a sclerosing reaction which may cause temporary or even permanent obstruction and atresia. Examples are given in Cases 3, 4 and 5.

Silent gallstones should always be operated upon when discovered despite a lack of symptoms. This dictum also applies to those individuals whose gallbladders fail to fill when x-ray studies are performed. It has been fully demonstrated that this inflammatory process frequently affects the bile ducts as well as the gallbladder resulting in fibrosis and atresia. The advisability of exploring the bile ducts during an attack of cholecystitis has been a matter of debate. It seems rational that this procedure be performed more frequently since dilation and drainage of the ducts would prevent cicatrization and possible atresia.

Summary

1. The etiology of stricture of the bile ducts is discussed.

2. Surgical principles in this clinical entity are evaluated.

3. Six case reports are given, illustrating the pathology and reconstructive methods.

4. A new operative technic which enables the surgeon to obtain mucosa-to-mucosa anastomosis which has been used by the author is described and illustrated. This is particularly valuable when dealing with a short duct.

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Discussion

Dr. O. H. Wangensteen:—Almost 30 years ago in preparing a paper on external biliary fistula (*J.A.M.A.* **93**:1199, 1929) I ran across an interesting paper written by a surgeon by the name of Ross, written from Los Angeles, as I remember it, on external biliary fistula. He reported a patient with a complete external biliary fistula who felt the need for bile to the extent that he drank his own bile from the collection bottle, while he ate his lunch at work. I wonder if that was the same Dr. Ross who has just presented this interesting paper on common bile duct injuries.

Dr. Ross:—That is right.

Dr. Wangensteen:—I am very glad to have the opportunity of finally meeting up with the author of that informative paper.

Dr. Snapper:—As I remember it, Dr. Ross said that he emptied his bile bottle, however bitter the bile may have been, and he drank it down without any adjuvant.

Dr. Ross:—That is correct. I have used it a lot since, and I am surprised that the patients tolerate it so well.

Dr. Wangensteen:—We used to hear a lot about external biliary fistula. J. B. Murphy wrote extensively about external biliary fistula and pointed out if a patient drained bile for a long time following drainage of the gallbladder, he undoubtedly had an impacted stone in the terminal end of the common bile duct; on the contrary, if mucus drained from the fistula following drainage of the gallbladder, the persistent obstruction was probably in the cystic duct.

Well, we do not hear so much about external biliary fistula today, and when we do, it concerns an even more serious problem: injury of the common bile duct at the time of cholecystectomy.

A paper is to be presented by Dr. Smithwick I note which will overlap somewhat with the paper now under discussion, and some of the discussion might well be postponed therefore until then. I should like, however, to endorse what Dr. Ross had to say about care in exposing the bile ducts and in determining upon a course of action before one embarks without extra thought on removal of the gallbladder. It is so easy to believe that the structure isolated is the cystic duct and to cut it. That final step should not be taken without exposing the "Y" of the common hepatic and cystic ducts. And if there is any suggestion of abnormality, no structure should be divided until one has actually determined what it is. If one cannot readily come to a satisfactory conclusion, it is wise to come down from the top, proceeding in part from one direction and then from the other in the dissection. The cholecystectomy by choice, of course, should be subserosal in nature, as described many years ago by Courvoisier of Basle. This can be a very simple procedure and yet, if one has a little trouble with the cystic artery, it can be a bloody business. Haste, as Dr. Ross has implied, is the usual causative factor in stricture of the common bile duct following cholecystectomy.

Just yesterday in the mail I had a letter from a Dr. Laube of Dubuque, Iowa, who wrote he had just seen a patient operated on in our hospital 35 years ago for a severe biliary stricture. I was an intern at the University of Minnesota Hospitals then. I still recall how deeply jaundiced this patient was and what a pitiable figure she was, just because her surgeon had done a hasty cholecystectomy. It is very pleasant to know that the corrective procedure performed by my preceptor and predecessor, the late Dr. Arthur Strachauer, 35 years ago has held up so well. That is not a mean accomplishment.

A few moments' inattention or haste can ruin and sometimes take the patient's life. Gallbladder surgery is intended to make a patient's life a happier and longer one; yet, a few minutes of thoughtless haste can wreak a lot of havoc.

Much could be said as to how such strictures should be repaired. If the accident is identified, the surgeon approximates the ends of the common bile duct and puts in a T-tube proximal to the site of suture.

If all of us here were surgeons and this was the field of special interest of all of us, there probably would be no common agreement amongst us over how the repair of the stricture should be made. The preponderance of opinion would probably favor suture of the proximal end of the common bile duct to the duodenum, employing fine catgut sutures for the inner row and interrupted silk sutures for the outer row in the anastomosis. There might even be differences of opinion concerning the length of the lower arm of the T-tube to be used.

Dr. Cattell, of this city, a very experienced surgeon of the biliary tract employs a long T-tube, with the lower arm extending into the duodenum. I do not favor the use of such a tube believing that it may exert pressure on the opening of the pancreatic duct into the biliary ampulla and thus potentiate the occurrence of pancreatic necrosis. I have discussed all this with Dr. Cattell, and I must say he makes a very good defense of his use of the long tube, and if he were here and I chose to argue the point with him, I would probably get the worst of it, yet, I feel it is not good to have an arm of an inlying T-tube ply over the outlet of the duct of Wirsung.

Pancreatic necrosis is a disease that we know relatively little about. Long years ago I spent some time working on the problem of pancreatic necrosis. You can do almost anything to the pancreas in the dog—you can cut it, bruise it, and nothing happens; on the contrary, in man if a biopsy is made of the head of the pancreas, death may ensue from pancreatic necrosis. It is not therefore only a matter of getting a good snug water-tight closure of an opening in the common bile duct, it is equally important to treat the pancreas and its ducts with profound respect. Why the pancreas of man is so sensitive to operative injury, as contrasted with the dog, is not known. The nature of the difference needs to be elucidated.

These are some of the things that the surgeon must think of in thwarting the occurrence of, and in undertaking the repair of common bile duct injuries. The slide of Dr. Ross' last patient was unusually interesting. Could you tell us Dr. Ross how long ago the operation was done, and what the present status of the patient is?

Dr. Ross:—The patient is well, without symptoms, after a lapse of two years.

Dr. Wangensteen:—Well, not bad!

Dr. I. Snapper:—The accidental discovery of gallstones when an x-ray is made for a complaint not connected with cholelithiasis is, in my opinion, no absolute indication for a cholecystectomy. Since these patients have carried their gallstones for a considerable time without any complaints, there is no reason why they cannot continue this for another 30 years. It is true that as a great exception a patient with an asymptomatic cholelithiasis suddenly may develop spiking fever due to an empyema of the gallbladder and that, even more rarely, a perforation of the gallbladder may occur as a bolt from the blue. These exceptional cases do not justify the removal of all asymptomatic gallbladders with stones because the sum total of all complications occurring in a large series of cholecystectomies in the form of thrombophlebitis, pulmonary infarction, cardiac arrest, etc., is not completely negligible.

The truth lies in the middle and careful weighing of the different indications and contraindications is necessary before an asymptomatic gallbladder with stones has to be condemned.

MEDICAL PROBLEMS IN BILIARY TRACT DISEASE*

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Many interesting problems in biliary tract disease have been investigated during recent years, but there is insufficient time today to discuss all of these. I shall concentrate on three of them—chlorpromazine jaundice, angina pectoris and gallstones, and the relation of calculus size to gallbladder disease.

Chlorpromazine Jaundice

Since the introduction of the valuable therapeutic agent chlorpromazine about five years ago an increasing interest has been focused on the occasional development of jaundice in patients receiving this drug. Because this jaundice has many aspects of obstructive icterus, the important differential diagnostic features between it and surgical jaundice are worthy of discussion. It is not an extremely rare complication of the use of chlorpromazine, clinical jaundice developing in somewhat less than one per cent and abnormalities in liver function tests particularly elevation in the alkaline phosphatase in almost five per cent[1] of patients receiving the drug.

The clinical features of the icterus are noteworthy. A history of ingestion of the drug is of course essential and every patient in whom the disorder is suspect should be shown the medication in its several forms in order to rule it out as the etiologic agent of his jaundice. While it is most common in patients on large and prolonged doses of the drug, icterus has been reported after taking only two tablets. The onset is most often two or three weeks after exposure to chlorpromazine, yet extremes of 2 to 60 days have been reported. Upon withdrawal of the drug the icterus clears in two to four weeks, but in ten per cent of such patients a prolonged course may ensue, lasting over three months[2]. In the average patient the bilirubin values rarely exceed 6 mg. per cent, yet in this protracted group higher values have been recorded.

Other clinical features of note in this syndrome are the frequently associated indigestion without severe pain, itching with or without urticaria, fatigue, chills and fever—symptoms frequently associated with biliary tract obstruction due to other causes. The liver is normal in size or very slightly enlarged. It may be tender. The spleen is not usually palpable.

The direct serum bilirubin is elevated and bile noted in the urine if jaundice is present. Elevation of the alkaline phosphatase to 10 or more Bodansky

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units is almost invariably recorded. Levels as high as 50 Bodansky units have been reported. The flocculation and turbidity tests are normal or only slightly elevated. A significant eosinophilia is very common. The bromsulfalein test is frequently elevated, even when the levels of icterus are minimal.

The diagnosis can of course be strongly suspected from these features, but often liver biopsy is necessary to establish the etiology of the jaundice. While the pathologist[3] can determine a characteristic and diagnostic appearance in about half of the patients from the intrahepatic bile stasis and eosinophilic pericholangitis, the presence of extravasated bile, bile infarcts, and intracanalicular microcalculi make extrahepatic biliary obstruction a distinct possibility. In such patients exploration is justified if a brief period of observation is not clarifying. Gambescia[1] believes that the pericholangitic eosinphilia and edema, the occasional rapid onset after ingestion of only a few tablets suggests a hypersensitivity response to the drug. Others believe that stasis in the microcanaliculi producing regurgitation, is a more likely explanation of this disorder.

In the vast majority of patients the icterus clears in a few weeks leaving a completely normal liver. The development in the prolonged cases of abnormal flocculation tests has led some investigators to consider the possibility of a superimposed infection of viral hepatitis in this group. Increased susceptibility to a viral agent during this type of jaundice has been discussed. It is in this sort of patient that residual liver disease might occur, and in whom death might rarely take place.

Angina Pectoris and Gallstones

In a group of patients of older age it is not surprising to find individuals who have both gallbladder calculi and arteriosclerotic coronary heart disease. During a recent five-year period at the Mayo Clinic[4] six per cent of the patients undergoing cholecystectomy had significant coronary heart disease. Since Babcock in 1909 claimed that chronic cholecystitis was a cause of myocardial disease, discussion has prevailed whether actual benefit to the heart resulted from operation on an asymptomatic gallbladder containing stones. There is no disagreement that the clearly symptomatic gallbladder should be removed, in the cardiac as well as the noncardiac patient. The Mayo Clinic reported approximately 25 per cent of those with both disorders noted improvement in their cardiac symptoms five years after gallbladder surgery, but a slightly greater per cent had died of their heart disease or were worse after the same period of observation.

How can one select the members of the group who might have symptomatic improvement over such a period? Since operative mortality is 2-3 times higher in this group, selection is indicated. Certainly, any patient with pseudo rather than real angina will be helped, particularly in the patient whose symptoms are due to reflex esophageal spasm triggered by the gallbladder. Patients whose

angina is related to cardiac arrhythmias are apt to obtain benefit. Stokes-Adams attacks may cease after cholecystectomy[5]. Stones in the common duct may set up reflex changes through the vagus nerve which reduces coronary blood flow and this type of patient may receive noteworthy aid from surgery. Reversal of electrocardiographic abnormalities in certain patients after operation, on the other hand, does not demonstrate anything more than what might be the natural course of their coronary disease.

In my experience there is a group of patients who have a symptom pattern which, I believe, suggests that they will benefit from surgery. Their angina is nocturnal or postcibal, rarely postexertional. Relief from the use of nitroglycerine is characteristic of the nocturnal episode appearing after a rich and fatty meal, accompanied by partial relief when sitting upright or walking about. In the male patient angina may be so severe as to prevent sexual intercourse in the evening, but it is not so disabling in the morning.

Anesthesia is an important factor in keeping the operative mortality of this group of patients as low as possible. Adequate airway and freedom from any hypoxia are essential. The phase of recovery during the first 24 hours is likewise important. Sudden death during operation or shortly thereafter usually follows a transient period of hypoxia, and if this has occurred, moving the patient from operating table to bed should be delayed until electrocardiographic evidence of freedom from ischemia has been obtained.

Calculus Size

I hope Dr. Wangensteen will say something about the recent experiences in his laboratory in producing gallstones in dogs by slightly narrowing the lower end of their common bile duct. Once formed, stones may or may not announce their presence by attempts to escape from the gallbladder. It has been well recognized for years that the small, multiple facetted stones were most apt to move, producing gallbladder, colic, and common duct disorders. This certainly holds under the age of 60 years. Over this age, however, serious complications from the single large calculus appear[7]. Acute cholecystitis in the elderly is more apt to develop from a single stone in the cystic duct. Gallstone ileus is rare below this age. Silent common duct stones in my experience have mostly been large single calculi in the older patient. All of these complications are very serious ones, and it behooves us to consider what one should advise a patient to do about surgery if asymptomatic gallstones are found unexpectedly during some procedure. If the physician takes into account the age of the patient at the time of stone discovery and recalls the dictum that 50 per cent of silent stones at age of 50 years will have clinical importance at age 65 years and adds the above facts of stone size and number to the basic dictum, he will be able to give reasonable accurate advice and counsel to his questioning patient.

Summary

1. The clinical picture of jaundice due to chlorpromazine is reviewed.

2. The relationships between gallstones and angina pectoris are presented. Types of patients in whom cholecystectomy might prove beneficial are discussed.

3. The clinical importance of the single large gallbladder stone in the elderly patient is stressed.

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SURGICAL PROBLEMS IN BILIARY TRACT DISEASE*

Drainage of the Common Duct

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Drainage of the common duct is commonly employed in the surgical management of a variety of disorders of the biliary tract. There are many reasons for draining the common duct as part of the operative procedure. One of the most important of these is to insure that the pressure, which must be overcome in order that the liver can secrete bile, is reduced as much as possible. This is particularly important in the management of the severely jaundiced patient.

In a recent study of bile drainage from the common duct following operations for disorders of the biliary tract, Rundle et al[1] measured the output

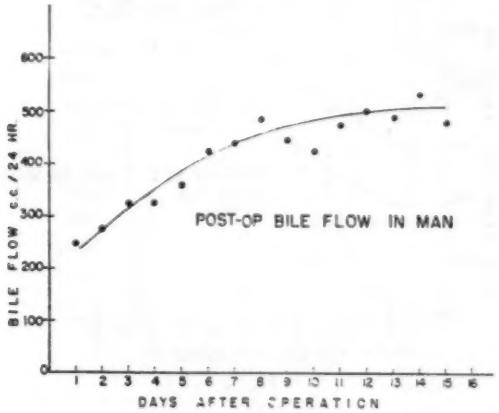

Fig. 1

of bile from day to day in the early postoperative period (Fig. 1). Data were collected after 27 operations involving 25 patients. The diagnoses were cholelithiasis in 20, hepatic cirrhosis in 2, carcinoma of the pancreas in 2 and chronic pancreatitis in 1. Before their operations many of the patients suffered from varying degrees of jaundice, cholangitis, and liver damage or dysfunction.

As indicated by Figure 1, the average output begins at about 250 c.c. daily and rises gradually to about 500 c.c. 15 days after operation. The 24-hour

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drainage ranged from 20 c.c. to 1,060 c.c. The average volume from the tenth day onward, when the flow leveled off was 478± 186 c.c. per 24 hours.

One of the interesting findings in this study was that drainage of the common duct results in virtually complete diversion of bile externally. Sixteen 24-hour specimens of duodenal aspirate from patients with T-tube drains in the common duct were analyzed for bilirubin content. Bile was absent from 12 and present in negligible concentration in four (less than 0.6 mg. per cent). Thus the fact was established that the resistance to the flow of bile externally through a T-tube is less than that which is required for bile to pass down the common duct through the ampulla of Vater and into the duodenum.

Another interesting observation was that the volume of bile draining externally from day to day is distinctly higher in patients having dilated ducts

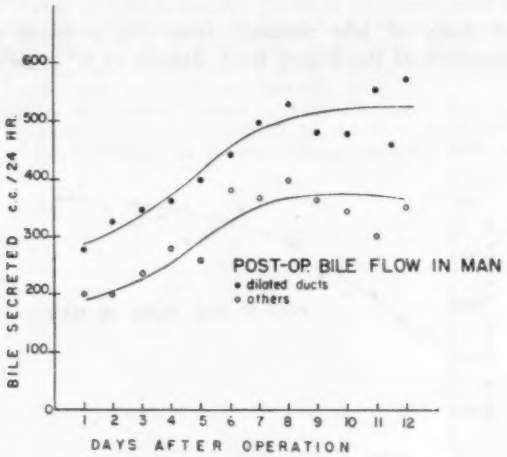

Fig. 2

by comparison with those having normal sized ducts (Fig. 2). As indicated by this figure, bile from normal sized ducts averaged from about 200 c.c. on the first postoperative day to about 350 c.c. by the tenth day. Bile drainage from dilated ducts on the other hand, ranged from about 300 c.c. at first to a little over 500 c.c. by the tenth day. In four patients with dilated ducts a release type of curve was noted with volumes of 800 to 900 c.c. in the early postoperative period before the drainage settled to the more usual level.

I should like to illustrate the importance of these two observations on drainage of the common duct in the management of biliary tract disease by presenting two case histories briefly. The first patient had extrahepatic jaundice due to a postoperative stricture of the common duct and the second patient had intrahepatic obstructive jaundice or so-called medical jaundice.

Case 1:—This patient was a 71-year old male who, 21 months prior to admission, had been operated upon for cholelithiasis. During the course of cholecystectomy his common duct was severed. The injury was recognized and the duct was reanastomosed over a T-tube. The T-tube was removed about three months after operation following which a bile fistula persisted for several weeks and then the external drainage ceased. He was well for about one month at which time he had an attack of jaundice with chills and fever of 102° F and marked itching. He was hospitalized, treated with antibiotics and his temperature subsided. The itching and jaundice persisted during the next 16 months varying in intensity, up to the time of his second operation. Prior to his second operation his liver was considerably enlarged and firm. His bilirubin was 12.2 mg./100 c.c., alkaline phosphatase 11.9 Bodansky units, prothrombin time 20 per cent, cephalin flocculation 3+, and thymol turbidity 7.5 units. At opera-

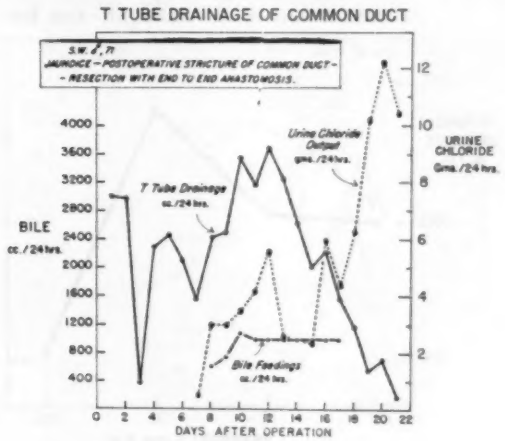

Fig. 3

tion an orange-sized pseudocyst was found arising from the strictured portion of the common duct. The latter was about 2 cm. in length. The cyst and stricture were excised and an end-to-end anastomosis of the duct was performed. The duct was drained with a T-tube so placed that the distal limb passed through the anastomosis but not into the duodenum. The duct proximal to the stricture was enormously dilated and contained bile under great pressure, as did the pseudocyst.

The postoperative course is illustrated by Figure 3. It shows the importance of the fact that drainage of the common duct results in virtually complete diversion of bile externally, and that in the case of dilated ducts the drainage may be excessive. Also, as in this case, there may be a release

type of curve with the secretion of extraordinary quantities of bile following the relief of the obstruction before the drainage settles down to the usual levels. In the first 24-hour period the bile drainage was 3,000 c.c. a most unusual quantity. Electrolyte replacement lagged behind the terrific loss which was taking place and within 24 hours the patient was in severe shock due principally to the loss of fluid and sodium chloride. A similar quantity was excreted the second day, but the implications with reference to replacement therapy were recognized and carried out. On the third day, the quantity of external drainage dropped sharply due to the fact that positive pressure was provided by elevating the T-tube for some 30 cm. at which point bile flow virtually ceased externally except for some increased drainage into the dressing. Presumably most of the bile entered the duodenum, but because of the hazard of either a localized or generalized extravasation of bile within the peritoneal

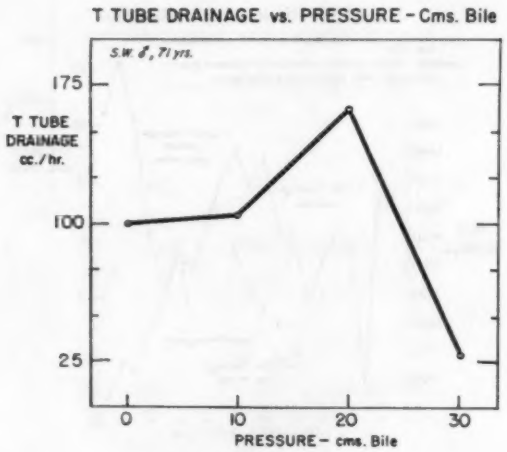

Fig. 4

cavity, we decided not to persist with this plan of management. From the fifth to the seventh day the bile drainage appeared to be decreasing but on the eighth day it began to increase again and by the twelfth day reached the extraordinary figure of 3,600 c.c. A urine chloride determination on the seventh day revealed a total 24-hour output of only 0.5 gm., a dangerously low figure, indicating that replacement therapy was not adequate despite the intravenous administration of tremendous amounts of salt, water and potassium. On the eighth day, bile feedings by nasal tube were commenced and continued in quantities of about 1,000 c.c. per day until the seventeenth day at which point the bile drainage was definitely on the wane. This was accompanied by a marked increase in urine chloride output which reached an unnecessarily high level as a consequence of bile feedings, decreased bile drainage and high salt

intake orally and parenterally. By the twenty-first day, bile drainage was at a reasonable level and the patient's convalescence was uneventful thereafter.

This case illustrates the hazards which may be associated with drainage of the common duct especially when it is tremendously dilated because of the completeness of diversion of bile from the intestinal tract and because of the tremendous quantity of the drainage in some patients. As indicated by Figure 4, on the third postoperative day it was found that if the resistance to bile flow through the T-tube was increased to 30 cm., external drainage dropped to a low level and the bile passed into the duodenum. This indicates that the resistance to the flow of bile through the ampulla of Vater into the duodenum may be considerably greater than that offered by a T-tube. This is one reason for considering drainage of the common duct in certain patients having intrahepatic or medical jaundice. This procedure was employed in the management of the second case to be presented.

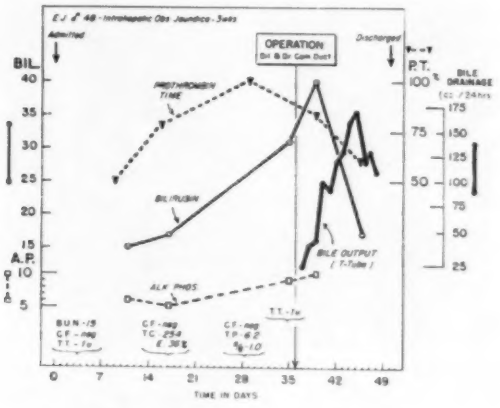

Fig. 5

Case 2:—This patient was a 48-year old male who entered the hospital for treatment three weeks after the onset of painless jaundice. Two weeks prior to the onset of jaundice the patient was given 25 mg. of Thorazine three times a day for four days because he felt depressed. The drug was stopped because of nausea. The latter disappeared promptly but recurred a week later and was associated with marked anorexia and fatigue (Fig. 5). Liver function tests carried out during the first week of hospitalization were all in keeping with a diagnosis of intrahepatic obstructive jaundice. The bilirubin was about 15 mg./100 c.c. alkaline phosphatase 6 Bodansky units, and the cephalin flocculation and thymol turbidity tests were negative. During the next four weeks his jaundice became progressively more severe. After five weeks of observation his bilirubin had risen 30 mg./100 c.c., the alkaline phos-

phatase increased somewhat and the flocculation tests remained negative. He was operated upon at this point, ten weeks after the onset of jaundice and five weeks after admission to the hospital. The preoperative diagnosis was intrahepatic obstructive jaundice and the primary purpose of the operation was to drain his common duct with a T-tube, so that the resistance to the flow of bile from the liver would be decreased. An additional reason for operating upon this patient was to make certain that the diagnosis was correct. On exploration, the extrahepatic duct system was found to be small, the ducts and gallbladder were collapsed as though they had been aspirated. There was no bile in any of the ducts and the epithelial surface of the ducts were beginning to adhere to each other. The common and hepatic ducts and the ampulla of Vater were gently dilated and the common duct was drained with a T-tube. Dilute pale bile began to drain from the T-tube within a few hours. The output was only 25 c.c. the first 24 hours. This increased each day reaching

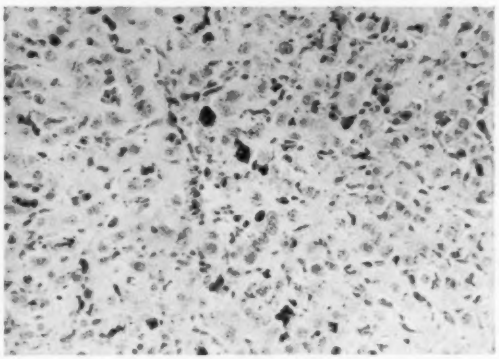

Fig. 6

175 c.c. on the ninth postoperative day. By the tenth postoperative day his bilirubin had fallen to about 15 mg./100 c.c.

After discharge from the hospital his T-tube was allowed to drain intermittently until his bilirubin fell to normal. This occurred nine months after operation. The T-tube was then clamped continually for one month. During this time he was asymptomatic, his bilirubin remained normal and a cholangiogram was normal. The T-tube was removed and the patient is in good health 18 months later. The liver biopsy (Fig. 6) showed the classical changes of intrahepatic obstructive jaundice due to Thorazine poisoning, with bile thrombi in the canaliculi, intracellular bile and bile in Kupffer cells, the abnormal process being confined to the central half of the lobules. We believe that this patient and other similar cases would not have recovered if their common ducts had not been drained.

Summary

1. Drainage of the common duct is frequently employed in the surgical management of a variety of biliary tract disorders.

2. It results in virtually complete diversion of bile from the intestinal tract because the resistance to the flow of bile through a T-tube is less than that offered by the common duct and the ampulla of Vater.

3. When the ducts are dilated, bile drainage may be excessive leading to severe electrolyte depletion if this possibility is not anticipated.

4. Certain patients with so-called medical jaundice, particularly of the intrahepatic obstructive varieties, will benefit from drainage of the common duct. This procedure should be considered in those patients whose jaundice is severe and is increasing. One probably should not delay operation more than four weeks in such cases.

5. Additional reasons for exploring such patients are that the diagnosis may be incorrect and, if correct, the extrahepatic duct system may also be involved in a process which can lead to complete occlusion.

6. Even if the extrahepatic ducts are normal, a severely damaged liver may be able to secrete bile externally when it cannot do so internally.

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Discussion

Dr. I. Snapper:—Both these papers have brought up points which for us physicians are of great importance.

Dr. Warthin has discussed the surgical treatment of gallstones in patients who have signs of coronary insufficiency. If, in a patient with coronary insufficiency and cholelithiasis, the diseased gallbladder causes complaints, the patient should be operated upon, in order to be relieved from his abdominal pains. Occasionally the coronary complaints may also be relieved after the operation. The latter favorable outcome is, however, uncommon.

Fortunately gallstone operations in patients with coronary insufficiency usually cause no special complications. This is due to the fact that when the surgeons know beforehand that a patient's cardiac condition gives rise to concern, more precautions are taken than when a patient with an allegedly normal circulation is operated upon! Thus, contradictorily, in the latter category of patients more unforeseen surgical accidents and complications occur than in patients with gallstones and coronary insufficiency.

As far as the differential diagnosis between coronary insufficiency and gallstones is concerned, it is correct that certain electrocardiographic anomalies prove the presence of coronary insufficiency. The reverse, however, is not true. Many patients with typical complaints of coronary insufficiency are reassured because for a long time the ECG, even after repeated two-step tests, is found to be normal. Only several months, perhaps years later, the course of events proves that as far as a correct diagnosis was concerned, the history and physical findings have been more reliable than the ECG.

In this respect it should also be remembered that radiation of pain caused by a diseased organ, situated below the diaphragm, cannot extend cephalad of the superior thoracic aperture. Therefore, if pains which could perhaps be ascribed to gallstones radiate to the neck or to the jaw, the source of the pain cannot be the gallbladder. In such cases the diseased organ must be located above the diaphragm and is usually either the heart or the esophagus.

As far as nocturnal pains are concerned, actually many patients with coronary insufficiency suffer mainly from nocturnal pains. During sleep the respiration becomes often superficial, less CO_2 is exhaled, and CO_2 accumulates in the blood. It is well known that inhalation of CO_2 can be used, instead of a two-step test, to cause precordial pains and changes in the ECG in order to prove the presence of coronary insufficiency. This explains at least partially why coronary pains may develop during sleep.

Relief in standing position is not a prerogative of patients with paraesophageal hernia. Many patients with angina pectoris always stand up when they have pain, evidently because they feel better in this position.

I fully agree with Dr. Smithwick that if a patient has jaundice of unknown origin, lasting for more than 4 to 6 weeks, an operation is indicated. One cannot completely rely upon our diagnostic battery of liver tests because it is well known that not too rarely gallstones are found at the operation—worse still at the autopsy—of jaundiced patients where no gallstones had been expected.

If, on the other hand in a case of jaundice of unknown origin, the cephalin flocculation is strongly positive and if the alkaline phosphatase of the serum is not significantly increased, then I might be inclined to wait somewhat longer than 4 weeks.

Surgical drainage of the common duct in jaundice due to hepatitis was popular 30 years ago and has come back again. It is remarkable that Rudolph Virchow, 80 years ago, considered that the disease we nowadays call hepatitis was actually a catarrhal jaundice which had led to the formation of a mucus plug in the common duct. This concept has been abandoned in the course of years and has been replaced by emphasis on the degenerative lesions in the

liver as the cause of the jaundice in hepatitis. The favorable influence, however, of drainage of the common duct in many cases of hepatitis seems to indicate that, apart from the intrahepatic degeneration, a slight obstruction of the common duct by a superficial inflammation and excessive mucus formation, may be a factor which should not be completely overlooked.

Dr. C. W. Wirts:—Dr. Wangensteen, I wonder if you would touch particularly upon this full-circle change of contemplated surgery of intrahepatic types of jaundice, such as chlorazine in catarrhal jaundice and hepatitis?

Dr. O. H. Wangensteen:—I wish I could reply to your suggestion, Dr. Wirts; however, the surgeon is rather limited in this sphere, and though I recognize and have a certain familiarity with some facets of the problem, many of the determinations and judgments come essentially in the province of the internist and concern items with which they have a far greater experience than a surgeon who treats obstructive jaundice. I have seen the identical situation that Dr. Smithwick talked of first. All the mental gyrations he went through, we went through, too. It is a difficult problem, but I believe if there is hazard of internal intravasation of bile, if the intraductal pressure is raised by elevating the bile bottle, it is probably playing the game more conservatively and safely to have the bile flow out than into the abdomen, until a firm fistulous tract has formed and all hazard of bile peritonitis is by. Meanwhile, as Dr. Smithwick indicated, there is a replacement problem which can assume extraordinary proportions. Concerning chlorpromazine jaundice, I cannot contribute anything worthwhile.

Gallstone formation, I have come to believe, is in many respects a mechanical problem. Dr. Warthin was good enough to foster this interest in my son who is a senior medical student at Harvard. When Steve came home last summer for his vacation, we found it impossible to keep him out of the laboratory. He seems to be intrigued by many facets of the problem. About four years ago, I began to notice how often the common duct is dilated in the presence of gallstones. In passing Bakes' dilators, if the smallest, which is 3 mm. in diameter, failed to pass, I began to make transverse duodenotomies with a view to examining the biliary papilla. Often, when stones were present in the gallbladder, an atretic biliary papilla was found—in fact, the papilla was often pinpoint in size.

My associates and I have just published [*Surgery* **42**:4:623-630 (Oct.), 1957] our first ventures with the production of gallstones by producing an *incomplete* stricture of the terminal common bile duct by the placement of a ligature of dicetyl phosphate, tied loosely around the terminal duct. In the course of a few weeks a stricture develops. Gallstones have been produced in monkeys, dogs, and in rabbits by this method.

Stones have been observed to follow as soon as five weeks following incomplete ligature of the common bile duct. If a stenosis of the cystic duct is

established simultaneously, one can produce calcium stones which are opaque to x-rays.

If the gallbladder is removed and the contracting ligature is applied, stones develop in the common bile duct.

One aspect of the problem that my son, Steve, was interested in was to see whether the administration of morphine to rabbits alone would bring about gallstone formation. We are also trying to ascertain whether the common bile duct may be dilated during the latter months of pregnancy. Because of the conjectured hazard to the fetus by x-ray irradiation, we have used intravenous injections of Biligrafin following delivery. As yet, we have failed to demonstrate any suggestion of common bile duct dilatation during pregnancy.

Now if gallstones result from a narrowed biliary papilla in man, what causes the contracted papilla? You will be interested in knowing that the common bile duct is about as sensitive to injury by digestive juices as is the squamous epithelium of the esophagus. In fact, the common bile duct will perforate if perfused with acid-peptic gastric juice as readily as will the esophagus. Glandular epithelium in general, as you know, is quite resistant to acid-peptic digestion. It was quite a surprise finding, therefore, to observe perforation of the common bile duct attending its perfusion with acid-peptic juice. It might well be too that bile and pancreatic juice may injure the bile duct and cause stenosis of the papilla. Yet we have failed to elicit perforation of the common bile duct following perfusion with mixtures of bile and pancreatic juice. We want to repeat this, however, using fresh bile from dog's gallbladders. Could it be that gastric juice gliding over the biliary component of the papilla within the duodenum may cause narrowing of the biliary papilla? Some of these questions cannot be answered today. I pose the question: Is cholecystectomy an adequate operation for gallstones? I am inclined to answer in the negative.

I would like to add a therapeutic item to the list of coronary artery problems mentioned by Dr. Warthin. Many of you will recall that John Hunter, who suffered from angina pectoris, a condition described a few years before by Heberden, died at St. Georges Hospital in London in such an attack, precipitated by a controversial discussion in a hospital staff meeting. It was debated whether he did have angina. At postmortem examination, it was found that John Hunter had gallstones as well as severe coronary artery disease. The relationship has been debated ever since. Present evidence would suggest that the relationship is coincidental. Hunter was wont to say it was the unpleasant excitements which provoked his angina, never the pleasant ones. Those of you, who go along readily with the thesis that angina pectoris is owing primarily to tension and increasing pressure of our times, may not be surprised to know that John Hunter said the same concerning the occurrence of angina in his day, almost two centuries ago.

Earlier this month I moderated a program at a meeting of the Surgical Forum in Atlantic City. The items suggested there for the relief of coronary disease were really intriguing. One of the important items, at least for surgeons who propose to bring relief to sufferers from coronary artery disease is to be certain of the diagnosis. There are conditions which masquerade as coronary disease which are not. I have seen a patient cured of coronary occlusion for which he was taking nitroglycerin daily, who has had no attacks since a cancer of his stomach was excised 10 years ago. Another patient who had an intractable ulcer needing surgical relief had a *status anginosus* accompanied by discernible electrocardiographic changes (at least interpreted as such) every time an operation was proposed. With her nurse-daughter's consent, I did a "sneak" gastric resection such as the late George Crile used to do for exophthalmic goiter. The patient survived for more than seven years thereafter and the gastric resection cured her angina.

A more recent experience with Dr. Paul Dudley White before a Congressional Committee emphasizes even more importantly the necessity for reliable criteria upon which to make the diagnosis of angina. There are moods of Congress like there are in ourselves, of course. This was March 1956 and Congress was of a mind to give Dr. White, for purposes of research, anything he would ask for. And those of you who know Dr. White will appreciate that he couched his petition in very appealing terms. The Committee said in effect: "Of course, Dr. White, you may have almost anything you want, but we want to take the time to tell you a little about ourselves."

A member of that Committee told this story. He said in effect, "For 14 years I carried nitroglycerin in my pocket. I took it every day. I consumed a lot of it. Then one day the Congress was shot up by political Puerto Rican insurgents. My spine stopped one of those bullets, but I think it did me good. I have never had any angina since, nor has it been necessary to take any nitroglycerin."

It might well be in order to declare a moratorium on operations for coronary artery disease—at least such operations should not be undertaken with adequate objective evidence of the presence of coronary artery disease. There is an important difference between testimony and evidence and we probably have had more testimony than evidence from a number of surgeons proposing to cure coronary artery disease by operation.

And so it seemed to me it was in the Surgical Forum session in Atlantic City. Toward the end of World War II, a surgeon in Turin, Italy, described the operation of ligature of the internal mammary artery that Dr. Warthin alluded to. We had just listened to a presentation purporting to show that ligature of the internal mammary artery was a highly successful procedure in bringing relief to patients who suffered from angina. In fact, Professor Dogliotti, now Professor

of Surgery at Turin, arose also to describe how popular and how successful this operation was in the hands of Italian surgeons today.

It was then I told the story of the Congressman and the bullet with ensuant relief from angina. A charming young lady in the audience came forward and asked for the privileges of the platform. She had done this same operation but her best results she found were in the group in which she had only gone through the motions but had not actually ligated the vessels. She got as you may well imagine a rousing ovation from the audience. I looked at the name on her lapel. It was Corrylos. I said, "Was your father Paul Corrylos?" She said, "It was." Genes do carry through!

Some of you undoubtedly knew Paul Corrylos. He was one of the most effective debaters I have ever heard in the medical field and in such controversies, testimony cannot compete with evidence.

In our Clinic, Alan Thal is emphasizing the importance of angiograms in making the diagnosis. He employs renograffin—an agent that does not produce spasm of the coronary vessels. He has made a large number of such injections without observing any suggestion of difficulty.

Thal makes an arteriotomy on the brachial artery in the upper arm. He seizes the endothelium of the vessel with mosquito forceps, threads the catheter in and makes the injection with a pressure apparatus. Obstructions and narrowing of the coronary arteries can be detected on the roentgen films.

We are in need of objective evidence upon which to base the diagnosis. In the absence of an episode of occlusion we should, I feel, be doubting Thomases about some of the operations which are invoked to cure coronary artery disease. It is easy to cure pseudoangina, but why perform an operation for its relief?

Dr. Snapper spoke of the circumstance that compensated patients with coronary artery disease stand operations well, when carefully performed. That too has been our experience.

Dr. Reginald H. Smithwick:—I find myself agreeing with almost everything Dr. Wangensteen has said. I also agree with Dr. Snapper that when the function tests originally give every evidence of primary liver disease, especially disease of the liver cells themselves, one should watch the patient longer. I did want to bring up this question of intrahepatic jaundice because it is something that is not discussed very frequently in my experience, yet I think there is a very clear indication for surgery in properly selected patients with this disease.

My experience is that there are patients who may die unnecessarily because they are not operated on, and I think one must realize that if you have a liver biopsy that gives a picture of intrahepatic jaundice of intracannicular variety or even involving the cholangioles, that that does not mean that the extra-

hepatic duct system is not involved; in fact, the disorder in the first place may have started in the extrahepatic system and secondarily involved the liver. So I think that where you have the picture of obstructive jaundice that is severe and increasing, somewhere in the region of four to six weeks is long enough to wait.

Dr. Thomas A. Warthin:—I should like to say only that I agree with all of the different comments.

In regard to operating on these people, if you have a classical liver biopsy of the allergic type of cholangitis with eosinophilic infiltration, you can be quite sure you have the chlorpromazine variety. I think Dr. Smithwick's is one of the atypical type that Dr. Snapper talked about, and in this case the patient certainly should be operated upon.

HEMATOLOGIC CHANGES IN CHRONIC LIVER DISEASE*

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A variety of hematologic changes have been observed during the course of liver disease. During acute or chronic liver disease associated with marked jaundice, for example, there appears a characteristic alteration in red cell shape, whereby the cell diameter increases, the cell surface increases without an increase in volume, and the cells appear flattened on microscopic examination, often forming target cells similar to those found in sickle cell anemia. Normal red cells have been shown to become similarly "flattened" after transfusion into jaundiced recipients. Like many of the hematologic alterations during liver disease, this red cell flattening is a curious phenomenon, not as yet understood, which is only of minor interest and is generally eclipsed by more direct manifestations of liver injury.

Disease of the liver of long standing, generally cirrhosis, may, however, become associated with two hematologic complications which at times may assume primary importance: first, an increased tendency to bleed; second, anemia. The hemorrhagic defects encountered in cirrhosis will be dealt with summarily since they vary greatly from case to case and are in general rather poorly understood. The most prevalent hemostatic defects demonstrable in patients with cirrhosis who bleed excessively are moderate reductions in platelet levels and in prothrombin concentrations; frequently these changes, which by themselves are usually insufficient to cause bleeding in an otherwise normal subject, are combined, and a tendency to bruise readily or to have epistaxes may result. When this situation complicates the presence of esophageal varices, gastrointestinal bleeding may become uncontrollable. In such situations transfusion with fresh whole blood in plastic containers, so as to best preserve the platelets, may be of value in acute control of the bleeding and in preparation for surgery. In exceptional instances, thrombocytopenia as a complication of cirrhosis may be severe, and may respond only to splenectomy. The precise mechanism of thrombocytopenia is not known, but most probably reflects excessive filtration of platelets by the large, congested spleens characteristic of cirrhosis, and is indeed most likely to occur in patients whose spleens are larger than usual for cirrhosis. Platelet levels may fluctuate widely in a given patient and a hemorrhagic tendency may only be evident, when these levels fall below a certain critical point. We have studied two patients with alcoholic cirrhosis in whom marked reductions in platelet levels occurred only after several weeks of heavy ingestion of alcohol. On each of such occasions these patients commenced to bruise and to bleed from the nose, gums and upper gastrointestinal

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tract. At these times moderately severe thrombocytopenia was the only serious hemostatic defect one could measure, and over a period of several days, platelet levels, and the hemorrhagic tendencies, slowly improved with no specific therapy. At present the mechanism of this phenomenon can only be speculated upon.

A great deal more, although by no means enough, is known about the pathogenesis of the anemias seen in chronic liver disease. Unless blood loss and iron deficiency have occurred, the anemia is almost always only mild or moderate in degree and of relatively little clinical importance. A large fraction of patients with long-standing, severe cirrhosis have either no anemia, or possess hemoglobin levels only slightly below normal—that is, not below 11 gm. per cent. Frequently the plasma volume and cardiac output of these patients are increased and a form of mild "hypervolemic" or "dilution" anemia may exist similar to that seen in pregnancy. In many cirrhotic patients, however, hemoglobin levels of between 7 and 11 gm. per cent are encountered, in whom blood loss or hypervolemia are not implicated. This anemia is almost invariably somewhat macrocytic, is associated with persistent moderate reticulocytosis, and may be considered the characteristic "anemia of liver disease". In our experience hemoglobin levels in this anemia almost never fall below 6 to 7 gm. per cent, no matter how serious the progression of liver disease, and hemoglobin levels invariably improve as liver function improves. The characteristic macrocytosis is generally moderate, with mean corpuscular volumes seldom exceeding 125 μ^3. Unlike the anemias seen with certain other chronic diseases, such as chronic renal disease or chronic infection, the anemia of chronic liver disease is to a large extent a characteristic hemolytic process. Thus one observes a persistent reticulocytosis, erythroid hyperplasia of the marrow, and increased urobilinogen excretion. Red cell survival is diminished. Normal red cells transfused into cirrhotic patients are destroyed more rapidly than normal as indicated in the first slide. As compared to the survival of red cells in a normal subject, normal red cells survive less well in patients with cirrhosis and anemia. The extent to which red cell survival is reduced varies, as might be anticipated, from one case to the next, and there is a rough correlation between the severity of the anemia and the rapidity of destruction. These studies indicate that there is an extracorpuscular process which destroys red cells in cirrhosis. Further studies of this mechanism carried out with the use of Cr^{51}-labelled red cells, and body-surface scanning for localizing sites of accumulation of radioactivity, indicate that there is a rather rapid removal of labelled red cells from the circulation. Simultaneous to the removal of Cr^{51} from the blood, an accumulation of radioactivity in the spleens of cirrhotic subjects is evident. Previous studies have indicated that this pattern reflects splenic sequestration of the red cells.

We thus believe that the major factor in the pathogenesis of the anemia of liver disease is an extracorpuscular hemolytic process, and that this results from excessive splenic filtration of red cells. This filtration is felt to be a consequence

of the diminished perfusing pressure of the splenic circulation in the face of portal hypertension, or, to use an established expression, of "congestive splenomegaly".

There can nevertheless be no doubt that red cell production is abnormal in liver disease. The macrocytosis, for example, since it is evident even in erythroid precursors, is evidence of a red cell production defect, as is the increase in basophilic stippling. Indeed, macrocytosis is a feature of liver injury produced in mammals other than man, as well as in amphibians. Rough estimates of hemoglobin production in patients with the anemia of liver disease indicate that, despite continued anemia, and thus anoxia, compensatory blood production seldom increases more than 2 or 3 times, whereas healthy individuals may produce hemoglobin at 8 to 10 times the normal rate in order to compensate for anemia.

During the last 25 years, a number of nutrients have been administered to cirrhotic patients with anemia, in the belief that faulty metabolism of certain foodstuffs, such as Vitamin B_{12} may exist. Indeed, in recent years it has become evident that liver injury is attended by the release of a variety of normally-intracellular materials including certain enzymes, iron, ferritin and Vitamin B_{12}. The serum levels of Vitamin B_{12} during acute carbon tetrachloride injury or acute hepatitis may, indeed, be elevated strikingly, and in chronic liver disease lesser elevations of Vitamin B_{12} levels are common. Despite these findings, however, Vitamin B_{12} administration has had no effect upon the anemia of liver disease, except in the presence of coincidental pernicious anemia.

In a study of patients with alcoholic cirrhosis and anemia we have, however, found occasional patients, perhaps 1 in 10 or 20, in whom a more severe form of anemia has developed, with hemoglobin levels falling as low as 3 or 4 gm. per cent. In these patients, unlike in the characteristic anemia of liver disease, stigmata of the so-called nutritional macrocytic anemias or megaloblastic anemias were evident; these included multilobed polymorphonuclear granulocytes, leukopenia, oval macrocytes and frank maturation defects of red cell and myeloid precursors in the marrow. If allowed to remain on a routine diet on the ward, these patients often manifested striking reticulocyte rises during the first week or two after admission. In careful studies on a metabolic ward of several patients, we were able to establish the following points about the megaloblastic process sometimes complicating cirrhosis. 1. Serum Vitamin B_{12} levels were normal; 2. urinary excretion of folic acid and of citrovorum factor were abnormally low; 3. marked hematologic responses occurred to small daily amounts of injected folic acid, and 4. in terms of urinary excretion studies there was a tissue depletion of folic acid.

These patients, like many patients with alcoholic cirrhosis, were generally on inadequate diets. In several patients of this type, however, dietary histories have not revealed inadequate diets and malnutrition was not manifest on physi-

cal examination. In two patients with apparent folic acid deficiency complicating cirrhosis natural sources of folic acid were given orally, after a suitable control period. There was an excellent response to yeast containing folic acid largely in conjugated form, and no additional response when deconjugated yeast, folic acid, or synthetic folic acid, were used. Thus no defect in the absorption or deconjugation of folic acid was demonstrated.

Thus, in our experience, folic acid deficiency, which is otherwise rare in our hospital population, occurs with unusual frequency in patients with cirrhosis and chronic alcoholism, albeit such cases still constitute a small minority of cirrhotic patients. It is important to recognize this complication when it occurs, since the anemia may become extreme and there may be other symptoms of folic acid deficiency including glossitis, cheilitis, esophagitis, and proctitis, and since this is a remediable problem. The pathogenesis may be simply that of an exogenous vitamin deficiency in most cases, but the possibility exists of a defect in folic acid utilization in chronic liver disease.

Discussion

Dr. I. Snapper:—The role the spleen plays in the etiology of acquired hemolytic jaundice was first brought to the fore by Eppinger of Vienna around 1914. He brought out that the anemia in liver cirrhosis with jaundice and a large spleen was at least partly hemolytic in character. He came to this conclusion because he found in the spleen of these patients marked erythrophagocytosis by the endothelial cells of the splenic sinuses. He then asked his surgical colleagues to perform a splenectomy in these patients and saw to his great satisfaction that the anemia disappeared. In this period the van den Bergh reaction was introduced into clinical medicine which led to a clearer concept of the hemolytic character of the anemia in pernicious anemia. Thus splenectomy was also tried for the treatment of pernicious anemia. It then appeared that several of these patients did well for several years after the operation before a fatal recurrence of the disease set in. It may be permitted to reminisce that these splenectomies were done in severely anemic patients whose hemoglobin had often gone down to 6 gm. per cent, at a time when neither blood transfusions or antibiotics existed, when the surgeons still washed and scrubbed their hands properly, but did not have rubber gloves, when masks were considered to be superfluous, when electrolyte balances were not done. Nevertheless the fatality of splenectomy in pernicious anemia was not great. The most frequent complication which even nowadays cannot always be prevented, was splenic vein thrombosis with ascites, occasionally also pancreatitis.

As far as the nutritional part of the anemia in liver disease is concerned, in the tropics I have always obtained the impression that a reduced intake of extrinsic factor of Vitamin B_{12} is of little importance in persons who manufacture a normal quantity of intrinsic factor in the stomach, that is in persons

with a normal hydrochloric content of the stomach. In the presence of a reduction of the formation of intrinsic factor by the stomach, however, as found in hypochlorhydria, a moderate decrease of the Vitamin B_{12} or folic content of the food which would have no influence in a patient with a normal amount of intrinsic factor, may already cause nutritional anemia.

MANAGEMENT OF HEPATIC COMA*

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A discussion of the management of any clinical syndrome entails a definition of the pathogenesis and of the physiological and biochemical disorders which reproduce the syndrome. Since this ideal cannot yet be achieved in any discussion of "hepatic coma", our present concepts of the management of this syndrome are of necessity, limited by our ignorance of the nature of the biochemical and physiological lesions involved. Nonetheless, our understanding of the disordered metabolism associated with disease of the liver and portal circulation has progressed to a point where we can attempt to outline a reasonable program of management with some degree of assurance that we are restoring the patient towards a more normal metabolic state.

It is becoming increasingly clear that the term "hepatic coma" comprises a number of different clinical syndromes and in all probability quite different patterns in disordered metabolism. For purposes of clarification and management, it is reasonable to divide this heterogeneous group, referred to as "hepatic coma", into two major categories—the "exogenous" and the "spontaneous". This particular classification implies that in the first group a neurological disorder is precipitated by some extrinsic factor and that in the second group, the development of the clinical picture of "hepatic coma" depends on a disorder of metabolism dependent primarily on failure of the hepatic parenchyma to carry out many of its synthetic and detoxifying functions which are essential for the maintenance of homeostasis.

These two main categories can be further subdivided into acute and chronic types. This definition depends on the rate of progress of the metabolic abnormality and in that sense, is an artificial, but nonetheless, a clinically applicable terminology.

The syndrome referred to as "exogenous hepatic coma" depends upon the introduction of nitrogenous material into a bacteriologically normal gastrointestinal tract in the presence of established portal-systemic collateral channels. On the other hand, the picture of "spontaneous hepatic coma" may appear and progress inexorably to a fatal termination without any appreciable source of nitrogenous material in the gut and without any recognizable portal-systemic collateral channels. The purest example of the first type is represented by the phenomenon of "meat intoxication" in the Eck fistula dog while the clearest example of the second type is the patient who dies in coma following a fulmi-

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nating attack of acute hepatic necrosis either of an infectious or toxic cause. It is apparent, however, that there are endless possibilities for combinations of these disorders. For example, the patient with Laennec's cirrhosis may give evidence of a progressive deterioration of liver function at the same time as the development of a portal bed block is leading to extensive portal-systemic collateral channels; in this type of patient, either type of clinical syndrome may appear either singly or in combination. Nonetheless, the distinction is clear enough at the present time so that for purposes of discussion, it may be better to take up the management of these two major types of "hepatic coma" separately.

The clinical manifestations of "hepatic coma" have been well described[1,2] and will not be repeated in detail in this report.

Exogenous Hepatic Coma

It is now well established that the patient or laboratory animal with extensive portal-systemic collateral channels, which have been constructed surgically or which have developed spontaneously as a result of a portal bed block, consistently develops a pattern of neurological symptoms upon the oral administration of a number of nitrogenous substances, the common denominator of which is the liberation of ammonia in the gastrointestinal tract through the action of bacterial enzymes[3-8]. These symptoms may range from a mild disorder in mentation to a deep unresponsive coma; this syndrome is potentially reversible without neurological sequela but may and often does lead to a fatal termination. There has been increasing evidence that this syndrome is in fact due to ammonia intoxication. Certainly, the symptoms are induced by the nitrogenous material liberating "ammonia" in the gastrointestinal tract, are dependent upon the existence of portal-systemic collaterals which by-pass the normal mechanisms of urea synthesis in the liver, are accompanied by elevations of ammonia in the peripheral blood, are reversible when the hyperammoniemia is reduced and the precipitating substance withdrawn, and may be reproduced in laboratory animals by the intravenous administration of urease[9]. This does not imply that the biochemical picture is clarified. It had been suggested and seems quite probable that the toxic action of ammonia is due to the removal of alpha keto-glutaric acid from the Krebs cycle[7,10] but at the moment this concept is still in the category of an attractive hypothesis. It is by no means clear as to what blood "ammonia" represents. Some authors have considered that the hyperammoniemia is comparable to the azotemia in kidney disease and bears no causal relationship to the symptoms[11,12]. Nonetheless, there is no other theory at the present time which conforms so well to the many recognized biochemical abnormalities associated with "hepatic coma" and it is probable that continuing study will clarify much of the confusion existing at the present time.

The syndrome of exogenous "hepatic coma" or ammonia intoxication is seen in its most typical form in the patient with a normal liver or well compensated

cirrhosis, who has large portal-systemic shunts either surgically constructed or spontaneously developed, who is subjected to an excessive nitrogenous load in the gastrointestinal tract. This "nitrogen" may be in the form of blood (usually from ruptured esophageal varices although sometimes from other sources of upper gastrointestinal hemorrhage), certain diuretics or an excessive dietary protein intake. From our knowledge of the genesis of this syndrome of ammonia intoxication, it is immediately apparent that treatment can be directed simultaneously in several different channels. It is apparent that satisfactory management would depend, in theory, on the restriction of the offending "nitrogen" and its removal from the gastrointestinal tract, the prevention of the breakdown of the nitrogenous material into ammonia, the prevention of the absorption of ammonia from the gut, and the binding of ammonia into a nontoxic substance or its elimination from the metabolic pool. This last form of therapy has aroused considerable interest and discussion. Weil-Malherbe[13] has described the role of glutamic acid in the ammonium binding mechanisms of the body. The first clinical report of the treatment of hepatic coma with intravenous sodium glutamate by Walshe[14] in 1953 was followed shortly by reports of other investigators[15,16,17]. There is little doubt but what the administration of glutamic acid has a rapid and considerable effect on restoring elevated blood ammonia levels towards a normal range. There is less consistency, however, in the reports of its effectiveness as a clinical tool. Obviously, the administration of glutamic acid has proved to be most effective in the exogenous type of hepatic coma in which control of the causes of the hyperammoniemia can be more easily achieved. The reports of the ineffectiveness of glutamic acid in controlling ammonia intoxication[18,19] has been due either to overly optimistic expectations that it would prove to be a panacea for the decompensated liver, or to failure of recognition of the fact that the ammonia-binding effect of glutamic acid is temporary and that these changes begin to reverse with the cessation of administration. Certainly, glutamic acid does not provide a replacement for the decompensated liver but it has proved to be an effective adjunct to the therapy of ammonia intoxication.

The experimental work of Greenstein and his collaborators[20] stimulated the use of L-arginine at a clinical level. Initial reports of the clinical use of this amino acid[21,22] have been most encouraging. Although the mode of action, clinical effects and associated biochemical changes are not yet clear, it appears to have an effective action on hyperammoniemia, utilizing a somewhat different mechanism than glutamic acid in lowering the blood ammonia. In all probability both of these amino acids may be used simultaneously or sequentially in the treatment of ammonia intoxication.

One could then summarize the clinical management of exogenous hepatic coma or ammonia intoxication under the following headings: 1. Withdrawal or restriction of the offending nitrogenous substance. This is not always as simple as it sounds since hemorrhage from esophageal varices is not as easily restricted

as the elimination of protein from the diet. Nonetheless, vigorous and early efforts to control hemorrhage or any other source of nitrogenous load are imperative. 2. Use of cathartics and enemas have proved to be helpful in eliminating the nitrogenous pool in the gastrointestinal tract. 3. The administration of antibiotics either orally or parenterally, has proved to be effective in controlling this type of hyperammoniemia by altering the flora of the gastrointestinal tract to eliminate the source of ammonia-producing enzymes. Neomycin has been most frequently employed although all the broad spectrum antibiotics have varying degrees of effectiveness in this respect. 4. The administration of L-glutamic acid either orally or parenterally in the form of sodium or potassium salt has, as discussed above, proved to be effective in lowering the blood ammonia either in the acute or chronic form of exogenous hepatic coma. No appreciable toxic effects have been noted and dosages have ranged from 25 to 100 gm. over a 24-hour period. 5. L-arginine has been administered as a hydrochloride and appears to be equally effective in lowering the blood ammonia and, since the mechanism of action is somewhat different from that of glutamic acid, it may be used in combination to correct this metabolic abnormality.

It should be emphasized that this full scale outline of therapy may be unnecessary in a large percentage of cases since most of the milder forms of exogenous hepatic coma will respond merely to withdrawal of the offending nitrogenous material. Nonetheless, in the case of rapidly developing ammonia intoxication from a massive nitrogenous load, it is well to utilize a full scale attack immediately since this abnormality may be rapidly fatal.

Spontaneous Hepatic Coma

This is a complicated group of patients whose basic problem is hepatic decompensation and who may present to the physician a complex series of related and unrelated metabolic abnormalities in varying combinations. For this reason it is extremely difficult to outline a logical form of therapy since our ignorance of the disorders associated with hepatic failure is still so great. Nonetheless, it is possible to generalize about commonly recurring biochemical and physiological disorders and to treat them with some degree of specificity.

The patients in this group may present as acute fulminating clinical problems caused by massive necrosis of hepatic parenchyma or they may present a more leisurely and subtle onset of neurological and general symptoms associated with a slowly progressive failure of hepatic function.

The role of ammonia intoxication in the genesis of this type of "hepatic coma" is far from clear. The peripheral venous blood ammonia levels in this group of patients is usually in the range of 100 to 150 mcg. per cent as measured by the modification of the Conway microdiffusion method. Rarely, will the ammonia level reach the elevations seen in the exogenous type of coma and therefore, very justifiable questions have been raised as to whether or not dis-

orders in ammonia metabolism play any role in this particular entity. At the present time we cannot answer this question with any degree of assurance. Very stimulating and important observations have been made on arterial-venous differences and on cerebral uptake of ammonia under these circumstances which suggest that a saturation of the central nervous system with ammonia must occur before symptoms develop[10,23]. Hypotheses involving the concept of pNH_3 as affected by the acid-base balance may prove to be of great importance; these would suggest that the proportion of free ammonia to ammonium ion is increased by a rising pH and that it is the free ammonia primarily which is toxic[24,25]. It is quite clear, however, that a nitrogenous load imposed upon a patient with a decompensated liver may lead to ammonia intoxication and is certainly hazardous in the extreme. Therefore, regardless of one's thoughts on the specific biochemical change, it is imperative that protein withdrawal or restriction be instituted as soon as the first insidious symptoms of "hepatic coma" appear. Whether or not one takes a more vigorous approach towards the treatment of hyperammoniemia, would depend on the level of circulating blood ammonia. Certainly, these patients with spontaneous hepatic decompensation may manifest a superimposed ammonia intoxication particularly if they bleed into the gastrointestinal tract as they so frequently do either from esophageal varices or merely as a result of a generalized failure of the clotting mechanism.

The importance of a high carbohydrate intake has been repeatedly stressed over the years on an empirical basis and is undoubtedly an important part of the clinical management. The maintenance of nutrition can be accomplished by the use of parenteral hypertonic glucose solutions to supplement feedings given orally or introduced through a soft, rubber inlying nasogastric conduit.

Fluid and electrolyte imbalance is an almost universal problem in patients with failing livers as manifested by the gross disorders in sodium metabolism and in the accumulation of ascitic fluid so commonly observed in this group. The frequency of low serum sodium is well documented and may be of itself a cause of coma. This has been an increasingly common phenomenon since the importance of sodium restriction in the treatment of ascites has been recognized. The administration of sodium will invariably increase the degree of fluid retention in patients with ascites but it is still essential to maintain a serum sodium near the normal range. Oliguria or anuria are frequently seen and may be associated with a hyperkaliemia which of itself may be a fatal complication. One cannot outline any consistent program for the management of fluid and electrolyte disorders in this group of patients because of the extreme number of variables involved. Several of more obvious facts can be stressed. Diuresis is important although attended by the dangers of rapid alterations in electrolytes. Both ammonium chloride and Diamox are hazardous because of the risk of ammonia intoxication and the use of mercurial diuretics probably represents the safest and most satisfactory way of increasing urine output. As a generalization sodium intake should be restricted but serum sodium levels must be main-

tained. Hypertonic saline solutions may be utilized to restore a very low serum sodium without adding to an already excessive water load.

Overwhelming infections are commonly the cause of death in patients with liver failure. The source of the infection may be in the lungs, the urinary tract or from a septic intravascular thrombosis attendant upon inlying venous catheters. All these potential sources of infection should be watched carefully and antibiotics utilized freely if there is any question of impending or actual sepsis. The use of antibiotics may have the added advantage of reducing the bacterial enzymatic activity in the gastrointestinal tract.

Studies on cerebral oxygenation in the presence of liver disease have given some substance to the empirical use of oxygen therapy as an adjunct to treatment[26].

Disorders in the clotting mechanism are extremely common in patients with advanced hepatic disease and usually represent disturbances at a number of different points in the mechanism of blood coagulation rather than any single easily remedial deficit. Therefore, while the administration of Vitamin K should be almost a routine in these patients, the administration of fresh blood has proved to be the most effective way of treating this type of multiple disorder of the clotting mechanism.

The use of thioctic acid[27] is based on so little specific biochemical information that the use of this substance cannot be recommended as yet in the treatment of "hepatic coma".

Adrenal cortical steroids have been advocated particularly in the patients with acute fulminating hepatitis but its value is open to considerable question and the recognized complications of the treatment may negate any possible gain.

Disorders of carbohydrate metabolism may be manifested in the patient with cirrhosis either as hyperglycemia with a diabetic type of glucose tolerance curve or occasionally as hypoglycemia in association with a severely decompensated liver or with the development of an occult hepatoma. Careful attention to and regulation of blood sugar levels, therefore, are an important part of the management of liver failure.

The clinical picture associated with hepatic decompensation may be thoroughly confused by the association of any of the facets of alcoholism or alcohol withdrawal. Keen and critical observation of the patient is essential to dissociate the metabolic effects of the decompensated liver from those of excessive alcohol or a withdrawal from previous excesses.

The results of therapy in spontaneous hepatic coma are much more discouraging than in the exogenous type but nonetheless, the fact that the liver has remarkable regenerative powers should encourage the physician to maintain

a meticulous, flexible and carefully organized therapeutic program regardless of how apparently hopeless the situation may seem at any given time.

Summary and Conclusion

The clinical syndrome of "hepatic coma" has been divided into an exogenous form which in its purest manifestation represents ammonia intoxication and into a spontaneous form which includes all the complicated facets of disordered metabolism associated with severe damage to parenchymal cellular function. It is recognized that these two divisions may overlap and co-exist but the distinction seems valuable in orienting the methods of treatment. The treatment of ammonia intoxication depends upon the withdrawal of the offending nitrogenous substance which has been introduced into the gastrointestinal tract, the vigorous cleansing of the nitrogenous pool, the utilization of antibiotics to eliminate the bacterial intestinal enzymes which are the source of ammonia production, and the use of glutamic acid and arginine because of their demonstrated ability to lower an elevated blood ammonia.

An outline of the treatment of spontaneous hepatic coma has been given based on the consideration that ammonia intoxication may play a role in this syndrome but based primarily on the recognition that multiple metabolic abnormalities may be associated with a failing liver. Principles of treatment should include the maintenance of nutrition, restoration of fluid and electrolyte balance, correction of disordered clotting mechanisms in the blood, treatment of disorders associated with excesses of or withdrawal from alcohol, maintenance of a normal blood sugar, maintenance of renal function, and the use of antibiotics to counteract intestinal enzyme activity and to prevent the overwhelming sepsis so commonly associated with hepatic decompensation.

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Discussion

Dr. I. Snapper:—The importance of the influence of ammonia in the causation of hepatic coma should certainly not be underestimated. It should at all times be realized, however, that a Laennec's cirrhosis is for all practical purposes a septal cirrhosis. In the fibrous septa connecting the small branches of the portal vein in the hepatic triangles with the central lobular veins, i.e., branches of the hepatic veins, blood vessels are always present. In other words, in liver cirrhosis substances which are carried by the portal vein can get to the cava system without having passed the liver parenchyma. This is the reason why ammonia, absorbed from the intestine, can reach the systemic circulation. In the colon many very dangerous poisons are formed, as for instance, phenol,

scatol, and indol, which under normal conditions are neutralized by the liver. Not only these three compounds, not only ammonia, but many other toxic substances present in the intestine must play a role in the intoxication which results from a decompensated liver cirrhosis, because they can reach the systemic circulation via the intralobular septa without being detoxicated by the liver cells. It is therefore certainly of great value to try and neutralize the ammonia of the blood as present in liver cirrhosis, as can perhaps be done by glutamine, perhaps by arginine. For the final handling of hepatic coma it will however be necessary also to consider many other intestinal toxic compounds present in the blood which cannot be determined as easily as ammonia.

Dr. O. H. Wangensteen:—It is obviously becoming increasingly difficult to distinguish a surgeon from an internist as all of you know. The internists have gone so far as to adopt the long robe of the surgeon as they walk down the corridors of the hospital and make their rounds. This is a very friendly gesture and one which all surgeons appreciate, I am certain. It is good to have from a surgeon the information which Dr. McDermott has just given us concerning some of the biological problems of jaundice.

Most of us appreciate that it is almost a miracle when a patient with hepatic coma gets well. I think a great many more patients die than recover when hepatic coma supervenes. Let us hope that this situation will change with improved knowledge. The nature of hepatic coma is still not a matter of general agreement.

Dr. McDermott alluded to the Eck fistula. It was Pavlov's contention that meat poisoning had a lot to do with the illness which developed in dogs, following the establishment of a connection between the portal vein and the *vena cava*. For years, I believe, this idea retarded the surgical development of portacaval shunts. Fortunately for medicine, Whipple and Blakemore took an aggressive attitude toward this problem somewhat more than a decade ago. Blakemore feels that advance of the surgery of portal hypertension was slowed a number of years ago when great emphasis in preparing patients with cirrhosis for operation was placed on the use of glucose. Blakemore feels strongly that the generous feeding of protein to these patients is important to make them safe risks for operation. He speaks of the era before and after Patek who made the strong case for high protein diets for patients with cirrhosis. The record of surgeons like Blakemore and Linton in the management of portal cirrhosis by portacaval shunts is an impressive one.

Dr. Mulligan, of St. Louis, reported in the Surgical Forum earlier this month, his experience of treating renewed hemorrhage in 10 per cent of patients with portal hypertension in whom portacaval shunt had been made at an earlier date. This observation led him to make Heidenhain pouches in dogs and study gastric secretion following the establishment of a portacaval shunt. Mulligan reported finding an enormous increase in secretion of acid from such

pouches and concluded that whereas a portacaval shunt may reduce the portal hypertension, it may have undesirable side-effects such as increased gastric secretion which, in turn, may potentiate the ulcer diathesis.

Dr. McDermott's studies are very timely. It is an interesting and fascinating field of inquiry and hope that he will continue his important studies. We certainly need a lot more light in this dark field.

Dr. William V. McDermott, Jr.:—I should like to thank Dr. Snapper and Dr. Wangensteen for their comments, which have been constructive, and so helpful.

I think Dr. Snapper has brought out the fact that, we tend to stress the minutiae we know and minimize the tremendous amount we do not know. The fact is, we are limited in our ability to measure such a thing as the toxic amines which we think are very important, in many instances, in the genesis of disorders associated with the liver. We are held up by ignorance and technical ineptitude, and other things which I hope will steadily resolve.

Dr. Wangensteen's comments about the portacaval shunt made reference to Dr. Mulligan's interesting work, which is extremely important. All of us in doing portacaval shunts recognize there are many ill effects from a portacaval shunt, and that all we do with a portacaval shunt is protect the patients from further hemorrhage, which seems to be pretty well established. The incidental, perhaps poor effects of a portacaval shunt we have to accept and try to manage the best we can.

I think between 10 and 20 per cent of our portal systemic shunts do show some effects of ammonia intoxication at one time or another, but with recognition of that, it is not ordinarily too difficult to manage. I think perhaps this increased secretory response of the Heidenhain pouch may explain some of the ulcers which we have seen after portacaval shunts, but the diatheses are so widespread it is hard to nail it to that. Statistically it will alert us and keep us thinking about this possibility in our shunt patients.

THE IMPACT OF ANTIBIOTICS ON THE GASTROINTESTINAL TRACT

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All of the presently employed antimicrobial agents may alter the normal physiologic and bacteriologic status of the gastrointestinal tract when they are administered orally. Some of these drugs produce the same effects even when they are given parenterally because they are secreted or excreted into the bowel. Two types of reaction may be observed: 1. Irritation of the gastrointestinal mucosa and 2. disruption of the normal microbial flora which may occur without untoward results or be responsible for a) superinfection or b) changes in some of the metabolic processes.

Almost all antibacterial drugs are capable of causing irritation in any part of the alimentary tract. Acute glossitis or stomatitis or both may follow the oral administration of penicillin, especially when it is applied locally to the mouth in the form of lozenges or troches. Irritation of the stomach is common with some of the antibiotics, but it may result from the ingestion of any of them. Nausea and vomiting are most frequent when paraaminosalicylic acid is given for the treatment of tuberculosis but are also noted often after oral therapy with oxytetracycline (Terramycin) and chlortetracycline (Aureomycin). Penicillin and various of the sulfonamide compounds may also provoke gastric irritation after being taken by mouth. In most instances, the symptoms are due to direct irritation of the gastric and duodenal mucosa. That various antibiotic agents are cellular poisons is indicated by the observation that cells in tissue cultures may be killed by exposure to some of these drugs.

Various antibiotics may also produce irritation of the intestinal tract. This may be due to direct action of the drug; in some cases, it results from the highly acid nature of the agent. The outstanding symptoms are abdominal cramps and diarrhea of varying degree. While the so-called "broad-spectrum" antibiotics are most frequently responsible for intestinal irritation, almost all of the antimicrobial agents presently in use may produce this effect when they are administered orally. In some instances, even penicillin may be highly irritative to the bowel and produce diarrhea when given in large doses by mouth.

The intensity of gastric irritation produced by antibiotics may be reduced by the administration of alkali or buffering compounds in many cases. Care must be exercised, however, in selecting the proper agent in some instances.

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Sodium bicarbonate is often helpful in decreasing the degree of nausea or vomiting or both which may follow the ingestion of paraaminosalicylic acid; the writer has found that a glass of milk taken after each dose of this drug is just as effective and more pleasant. Aluminum hydroxide should not be given to combat the irritative effects of the tetracycline compounds because it interferes with their proper absorption. The use of antacids containing magnesium to counteract the irritation produced by the tetracyclines is contraindicated because this ion, in small quantities, abolishes the antibacterial activity of these agents. In some cases, gastric irritation is so severe and so little affected by the use of buffering substances that it becomes necessary to stop giving the antibiotic because the untoward reaction may produce more difficulty than the infection for which therapy was instituted.

Diarrhea is one of the most ominous symptoms resulting from the exhibition of antimicrobial agents. While it is simply irritative in origin in many instances and can be relieved by the administration of opium derivatives, the possibility that it is the result of changes in the intestinal microflora must be considered in every instance and the necessary steps taken to establish the presence of a superinfection promptly.

The oral or even parenteral administration of all antibiotics is practically always followed by changes in the character and numerical distribution of the bacteria normally present in the intestinal tract. The degree of change and the types of organisms which become predominant are directly related to the antimicrobial "spectrum" of the drug being administered. Agents with a relatively narrow range of activity, penicillin for example, produce less pronounced alterations in the normal intestinal microflora than those with a wide "spectrum"; the latter may suppress all but one or two components of the bacterial population. In many cases, the bowel flora returns to a normal pattern despite continuation of administration of the antibiotic. This results from the development of drug-resistance in the organisms while they are exposed to the drug and is particularly true when streptomycin is given because insensitivity to this agent develops rapidly. The greatest degree of suppression of the microbial population of the intestinal tract follows the simultaneous use of several antibiotics. Although it has been claimed that this produces complete sterilization of the bowel, it has not been possible to substantiate this in many instances. Changes in the type and number of intestinal bacteria following the administration of antibiotic agents are of no clinical consequence in most patients. In some, however, such alterations are followed quickly by invasion of the intestine by the organism which has become predominant and the appearance of a so-called "superinfection".

The most common and serious superinfection of the intestinal tract which results from the administration of antibiotics is acute staphylococcal enteritis. This is due to suppression of the bulk of bacteria in the bowel and outgrowth of *Staphylococcus aureus;* it is characterized by fever, profuse diarrhea (often

bloody), and a varying degree of prostration. In severe cases, shock may supervene rapidly. Occasionally, the organisms penetrate the blood stream, bacteremia follows, and metastatic foci of infection such as brain abscesses, meningitis, suppurative arthritis, and acute endocarditis may appear. Death may occur if the syndrome is not recognized early and treated promptly and intensively with an effective antimicrobial agent.

The simplest method of detecting acute staphylococcal enteritis is examination of a gram-stained smear of the liquid feces. This reveals clusters of gram-positive cocci alone or together with a small number of gram-negative bacteria. Cultures of the intestinal discharge yield coagulase-positive *Staph. aureus* as the only organism or as the predominant one. The presence of a few colonies of staphylococci in a stool culture is not diagnostic because small numbers of this organism are commonly present in the intestinal tract of normal individuals. The fecal discharge in cases of staphylococcal enterocolitis usually contains blood and polymorphonuclear leucocytes.

Treatment must be initiated immediately after the diagnosis of staphylococcal enteritis is established. It is obvious that the drug being administered at the time the diarrhea started must be discontinued. Since most strains of *Staphylococcus aureus* are sensitive to bacitracin and neomycin, either of these agents should be given until the organisms have been examined for their susceptibility to various antibiotics. It has been the writer's practice to give as much as one gram of bacitracin per day or 100 mg. per Kg. of body weight of neomycin in divided doses per day as soon as the possibility of staphylococcal enteritis is seriously considered. Neither of these agents is absorbed appreciably from the intestine and the untoward reactions which they may produce are, therefore, not a threat in this situation. Chloramphenicol plus erythromycin (0.5 gm. of each orally every 6 hours) is satisfactory therapy in many cases; the sensitivity of the responsible strain to these agents must be established. Treatment should be continued for at least two weeks.

Diarrhea following the use of antibiotics may be associated with so-called pseudomembraneous colitis. This is characterized by extensive necrosis of the bowel wall. Bacteriological studies of the feces frequently reveal *Proteus* and *Pseudomonas aeruginosa* as the predominant or only organisms; a few *E. coli* may be present. Severe generalized abdominal pain, fever, and a varying degree of prostration are common and shock and death may supervene when the disease is severe. The intestinal discharges contain blood and leucocytes in most cases. A preponderance of *Staph. aureus* is not present; this organism is usually completely absent. In some instances, bacteremia with *Proteus* or *Pseudomonas* or both may develop. Most important in the management of pseudomembraneous colitis, is discontinuing the antimicrobial agent which provoked its appearance. Very often this is sufficient to eliminate the disease. When the diarrhea persists, the administration of antibiotics to which the bowel organisms are

sensitive is indicated. It must be stressed that pseudomembraneous colitis was known to occur prior to the antibiotic era and some observers have questioned the role of these drugs in this syndrome. Diarrhea developing during therapy with antibacterial agents may be mild and continue for a variable period of time after treatment has been stopped. Microbiological studies of the intestinal contents reveals *Candida (Monilia)* in some patients; in many, it is absent. It is usually impossible to establish a causal relationship between these organisms and the diarrhea. The mere presence of *Candida* in feces does not indicate a specific etiologic role because it frequently increases in number when diarrhea is present. In sprue, for example, *Monilia* appears in large quantities in the stools of many cases. If the diarrhea becomes very severe and *Candida* is present in large numbers in the feces, a trial of nystatin (Mycostatin) therapy is worthwhile.

Superinfections of the intestinal tract are most frequent after the use of "broad-spectrum" antibiotics or mixtures of drugs. Although, at first glance, this appears paradoxical, the fact is that the more broad the antibacterial effects of a single or combination of agents, the greater is the reduction in number and types of the normal intestinal bacteria and the more likely the possibility that a single organism like *Staph. aureus* will emerge to become predominant and produce disease if it happens not to be sensitive to the antibacterial agent being administered.

Changes in the intestinal flora secondary to the administration of antibiotic agents may be responsible for adverse metabolic effects. Thus, it has been noted that patients receiving large quantities of single "broad-spectrum" drugs or combinations of antimicrobial substances sometimes develop a marked decrease in prothrombin and even bleed spontaneously. This is in all probability due to a reduced production of Vitamin K in the intestine as a result of suppression of growth or complete elimination of some of the components of the normal bowel flora. This phenomenon is readily reversible by the administration of Vitamin K_1 oxide.

Alteration in the intestinal flora occasionally results in a marked decrease in the quantity of fecal and urine urobilinogen because these are produced by bacterial activity. This may be responsible for a diagnostic paradox since patients with hepatocellular disease who are given antibiotics may have no demonstrable urobilinogen. In the presence of jaundice, this may lead to a mistaken diagnosis of biliary tract obstruction.

It has been clearly demonstrated that the administration of average therapeutic quantities of the tetracycline compounds to normal people leads to the development of negative nitrogen balance and the rapid excretion of riboflavin. Although not proved, these physiologic disturbances may be related to changes in the intestinal bacterial flora provoked by antibiotics. Steatorrhea has been noted during the administration of "broad-spectrum" drugs. The significance of

this phenomenon is not clear; its relationship to malabsorption snydromes is an interesting possibility for speculation.

Proctitis and pruritus ani follow the use of antibiotics, especially the "broad-spectrum" drugs in some patients. Both may be very prolonged and persist for months after the administration of the responsible agent has been stopped. They may be very difficult to treat. Although the exact mechanism of these syndromes is not known, the possibility of hypersensitization merits consideration.

In summary, it must be pointed out that the administration of any antibiotic agent, especially by mouth, may have an intense impact on the gastrointestinal tract. The minimal effect is an alteration in the microbial flora; this is a universal occurrence but of no clinical consequence in the bulk of patients. In some individuals metabolic disturbances may follow such changes in the intestinal bacteria. In a few cases, serious and potentially lethal superinfection of the bowel, *Staphylococcal enterocolitis* for example, may supervene. These phenomena are observed most often when "broad-spectrum" antibacterial agents are given orally. They may follow the oral or parenteral exhibition of any antimicrobial agent.

It is important to stress the fact that the risk of development of a gastrointestinal complication from the use of antibiotic agents should not deter the physician from employing these drugs in all situations in which they are definitely indicated. Any potent therapeutic agent may produce reactions. If, however, the dangers outweigh any possible benefits, a drug should not be given. This rule must guide the administration of all antibiotics.

Discussion

Dr. Edward Kass (Boston, Mass.):—It is difficult, when discussing a paper such as Dr. Weinstein has just given, to try to find any aspect of the subject that is not covered.

There are only a few small comments that I might make, simply to underline what Dr. Weinstein has said. One aspect of the use of the so-called broad spectrum antibiotics, is not often given as much recognition as might be warranted, and that is the effect of the administration of these agents on nitrogen balance. A few years ago Gabuzda and Jackson studied undernourished patients who were in positive nitrogen balance after being given a nutritious diet. When a tetracycline antibiotic was administered (the patients were not ill), there was a marked increase in nitrogen loss, preceded by riboflavin loss that was quite striking and reproducible, and often preceded by a loss of potassium in an amount that could not be explained entirely on the basis of nitrogen loss.

As soon as the antibiotic was discontinued, the patients returned to positive nitrogen balance. That this effect was not due solely to the effect on the bac-

terial flora of the intestines was shown in several ways. In the first place, the changes in bacterial flora were not striking although anaerobes were eliminated. Furthermore, when these experiments were repeated, and patients were given a combination of bacitracin and polymyxin by mouth instead of the tetracycline antibiotics, profound effects on the bowel flora were noted but there were no changes in nitrogen metabolism or in weight of the patients. Thus, profound effects on nitrogen balance were induced by administering tetracyclines to normal patients. Similar observations have been made by Faloon using chloramphenicol.

I mention this only to indicate that there are many effects of antibiotics that we have just begun to look into. Of course, we have spent most of our time worrying about the interaction of the drug and the organism, and relatively less about interaction of the drug and the host, except as obvious toxicity or hypersensitivity appeared. Now that we are reaching a plateau in the study of the organism's response to the drug, we can afford to take a closer look at the host response.

Another series of observations that might be underlined further has to do with the curious natural history of staphylococcal diarrhea and dysentery. A few years ago a house officer, who had contracted amebiasis during the war, wished to rid himself of amebae by therapy with one of the tetracyclines. We induced him during this time to count the number of bacteria in the stool using different concentrations of drug in agar plates, so that he would have some crude quantitative idea of what he was doing to the stool flora while following the number of amebae. During the first seven days he did not have an unusual change in bacterial flora. His total bacterial count fell from the initial level to approximately one hundred million organisms per gram of feces to the level of about a million. I would point out that in some of the literature this would be reported as a 99 per cent reduction in bacterial count. The organisms were increasingly resistant to the drug he was taking. On the eighth day, the gram stains showed only gram positive cocci to be present in the feces, a finding toxoid, that most of us would consider to be an ominous sign.

At this time there were no changes in bowel habits or in his sense of well-being. I am afraid some of the rest of us showed worse symptoms than he did. The number of bacteria at this time turned out to be ten billion bacteria per gram and they were all staphylococci. Although we wished to discontinue treatment and let his bowel flora return to their former condition, he thought he would treat the disease and not the bacteria, and would persist in the course of therapy.

The following day there was still no change in the bowel flora and the number of bacteria was exactly the same, with staphylococci exclusively, and no change in bowel habit, clinical behavior, or any other aspects of the clinical situation occurred. By the third day after the staphylococci first appeared there

was nothing but *Proteus* in the stool (about a hundred million bacteria per gram) and for the next few days nothing but *Proteus*.

I cite this to illustrate the fact that there may be total replacement of bowel flora by staphylococci in numbers that would ordinarily be ominous and yet have absolutely no clinical change accompanying this.

We don't know how common is this asymptomatic replacement of one bowel flora by staphylococci. At the other extreme are cases like the ones Dr. Weinstein cited, in which there may be spread from the bowel, with peritonitis, endocarditis, arthritis, meningitis, and so on, in which the mortality is great and therapy still not satisfactory.

In closing, once again may I express my appreciation to Dr. Weinstein for his excellent discussion of an important clinical problem.

TREATMENT OF GASTROINTESTINAL DISEASES WITH AN ANTICHOLINERGIC AND TRANQUILIZERS

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Emotional stress, manifested by tension and anxiety, is thought to be one of the important predisposing or precipitating factors in the development of peptic ulcer[1-3]. Ideally, these stress-producing factors in the patient's life situation should be eliminated, but this ideal is often impossible to achieve. Therefore, many gastroenterologists use various agents to modify the patient's response to stress, and prescribe sedatives or tranquilizers along with anticholinergics.

TABLE I

DIAGNOSES AND THERAPIES

Diagnosis	Number of patients	
	Prantal, Serpasil	Prantal, Trilafon
Duodenal ulcers	121	62
Gastric ulcers	9	9
Hiatus hernia with esophagitis	9	8
Jejunal ulcer following subtotal gastrectomy	5	7
Chronic gastritis	—	4
Chronic gallbladder disease	—	3
Ulcerative colitis	—	1
Duodenal and gastric ulcers	—	1
Totals	144	95

Barbiturates were used frequently in the past and are still prescribed widely. Daytime sedation is a common complaint, and the risks of habituation and overdosages are always present.

The newer nonbarbiturate tranquilizers are markedly superior since they are believed to be nonhabituating and act selectively to reduce anxiety without diminution of alertness.

*The Prantal and Trilafon used in this study were provided by G. Kenneth Hawkins, M.D., Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

The rauwolfia derivatives, notably reserpine, are prescribed occasionally for patients with gastrointestinal diseases. There is, however, some evidence that reserpine increases gastric acidity[4,5] and therefore it may be contraindicated in patients with peptic ulcer or a history of this disease.

The phenothiazine tranquilizers are very useful since they are safe and effective when administered properly and have no side-effects which would be special hazards among patients with peptic ulceration. They can be used to treat the emotional component with little risk of habituation or elevation of gastric acidity.

TABLE II

RADIOGRAPHIC STUDIES AFTER ONE MONTH OF THERAPY

Diagnosis	Number of pts.	Drugs and daily dosage	Healing	
			yes	no
Duodenal ulcers	4	Prantal 400 mg. Serpasil 0.4 mg.	3	1
Gastric ulcers	6	Prantal 400 mg. Serpasil 0.4 mg.	3	3
Duodenal ulcers	6	Prantal 400 mg. Trilafon 16 mg.	4	2
Gastric ulcers	9	Prantal 400 mg. Trilafon 16 mg.	9	0

MATERIALS AND METHODS

The drugs used in this study were Prantal® (diphemanil methylsulfate), Serpasil (reserpine), and Trilafon® (perphenazine). They were administered to 239 patients, most of whom were middle-aged, with acute or chronic gastrointestinal diseases. All were ambulatory.

Prantal is a quaternary ammonium compound with a specific anticholinergic effect on the parasympathetic nervous system[6]. It is used in peptic ulcer patients to diminish gastric secretion and acidity and its efficacy in reducing pain and enhancing healing has been amply confirmed clinically[7-11].

Serpasil is primarily a hypotensive agent; its tranquilizing effect makes it suitable for use in conditions associated with tension and anxiety[12].

Trilafon, an agent with tranquilizing and antiemetic properties similar to chlorpromazine, was selected from among other phenothiazine compounds because of its increased potency and relative freedom from side-effects[13]. Early clinical trials have been extremely promising among ambulatory patients with anxiety complicating somatic illness[14-17].

The primary purpose of this study was to discover any difference in effectiveness or tolerance between the two tranquilizers, all other factors being as nearly as possible equal.

Prantal, 100 mg., and Serpasil, 0.1 mg., were administered 4 times daily to 144 patients; 95 received Prantal, 100 mg., and Trilafon, 4 mg., 4 times daily. Of the latter group, a few originally received Prantal, 200 mg., and Trilafon, 4 mg., 4 times daily, but this dosage of Prantal was too high and therefore it

TABLE III

CHANGES IN GASTRIC ACIDITY DURING THERAPY

Diagnosis	Number of pts.	Drugs and daily dosage	Decreased	Unchanged
Duodenal ulcers	15	Prantal 400 mg. Serpasil 0.4 mg.	11	4
Duodenal ulcers	15	Prantal 400 mg. Trilafon 16 mg.	7	8
Gastric ulcers	9	Prantal 400 mg. Trilafon 16 mg.	5	4

was halved for the duration of the study (Table I). Duration of therapy was between 1 and 4 months but clinical evaluations of all patients were performed after 1 month.

Radiographic studies were made in 10 patients with duodenal ulcers and in 15 with gastric ulcers before and after 1 month of treatment. Ten patients received Prantal and Serpasil, and 15 received Prantal and Trilafon.

Analyses of gastric acidity were performed in 30 patients with duodenal ulcer and 9 with gastric ulcer before and after 1 month of treatment. Fifteen patients received Prantal and Serpasil, and 24 received Prantal and Trilafon.

RESULTS

Improvement occurred in all but 6 patients (4 with duodenal ulcers and 2 with jejunal ulcers) after 1 month of therapy with either combination. Clini-

cally, there was no significant difference in efficacy between the combinations studied.

Of the 10 patients who were studied radiographically after 1 month of therapy with Prantal and Serpasil, 6 showed evidence of healing. Of the 15 who received Prantal and Trilafon, 13 showed healing after 1 month (Table II).

None of the 39 patients tested showed any increase in gastric acidity during the treatment period. In 23 the level was decreased and in 16 it was unchanged. The fact that Serpasil did not elevate gastric acidity in any of these patients is probably due to the low doses used. We had no reason to believe that Trilafon might have an unfavorable effect on this value (Table III).

Both combinations, Prantal with Serpasil and Prantal with Trilafon, were very well tolerated. Side-effects possibly due to Trilafon occurred in 4 of the 95 patients who received this drug: restlessness was noted in 3 and 1 patient complained of generalized malaise. Prantal produced mild xerostomia in approximately 25 per cent of the 239 patients. Five of this group also experienced visual blurring. Xerostomia and visual blurring were more frequent with dosage schedule of Prantal, 200 mg., and Trilafon, 4 mg., 4 times daily. These reactions disappeared or were minimized when dosage was lowered.

Summary

Prantal and Serpasil or Prantal and Trilafon were administered to 239 patients with gastrointestinal diseases. The usual daily dosage of Prantal was 400 mg.; of Trilafon, 16 mg.; of Serpasil, 0.4 mg.

Both combinations were well tolerated and both provide excellent conservative therapy of peptic ulcers and other gastrointestinal diseases. We believe that Prantal and Trilafon is the combination of choice since the latter agent is as effective as reserpine in reducing the emotional component without the added risk of increasing gastric acidity.

In our experience the optimal daily dose of Prantal is 400 mg.; above this level xerostomia sometimes occurs. Although we used 16 mg. Trilafon daily with relative freedom from side-effects, we believe that 8 mg. is the optimal daily dose with which to initiate therapy. Dosage of both agents can be increased safely if necessary.

Conclusion

A combination of an anticholinergic drug (Prantal) and a tranquilizer (Trilafon) is advocated to replace the usual combination of an anticholinergic drug with a barbiturate. Evidence is herein adduced which demonstrates the value of administering Prantal together with Trilafon in the therapy of peptic ulcer.

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THE ROUTINE POSTOPERATIVE USE OF STANDARDIZED SENNA WITH A WETTING AGENT AS A BOWEL EVACUANT

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Senna, in many forms, has been used for medicinal purposes since the ninth century at which time it was prescribed by Arabian physicians. Chemically it belongs to the anthracene group of purgative drugs. It was not until 1936 that Straub found that the active glycosides of Senna contained anthracene.

The active glycosides of Senna are obtained from the pericarp of the pod. Chemically and biologically they may be standardized. Commercially these standardized principles have been incorporated into a palatable base of cocoa, malt and sugar, known as Senokot.

In a previous study by Dr. Robert Ehrlich and the author, of 122 patients, the efficacy of Senokot alone, in treatment of functional constipation, was conclusively demonstrated. It was also noted in that study, however, that certain untoward effects such as abdominal cramps and transitory diarrhea could not be avoided in a small number of the total, or the drug *per se* was ineffective.

At the time of this previous study, the authors had also noted that good results were obtained with the so-called wetting agent, Dioctyl Sodium Sulfosuccinate (DSS) in some patients with functional constipation. Therefore, it was decided that an excellent solution to the entire problem of constipation would be a combination of these two drugs and especially in the so-called resistant group. It is for this purpose that 100 hospitalized patients were selected at random and given standardized Senna with DSS* for relief of their constipation.

It is a well established fact that Senokot in itself confines its action to the colon—it being a standardized preparation of *cassia acutifolia* (Senna) pods. It is standardized by biological and chemical assay so that its action is known and predicted. This so-called purified end-product does not contain resinous matter which in itself causes untoward side-effects such as griping, etc.

The pharmacological action of Senokot is based on its three components namely, three active glycosides which are absorbed in the upper bowel, transported and then released via the blood stream into the large bowel. It is at this point that bacteria releases the active principle of the glycosides which then stimulates or activates Auerbach's plexus or the parasympathetic nerve supply which in turn initiates large bowel peristalsis. This physiologically timed

*The preparation used in this study was Senokap, supplied by the Medical Department of The Purdue Frederick Company.

evacuation of the colon usually requires from eight to ten hours following oral ingestion of the Senna principles.

A stool softener, or wetting agent, acts only on the consistency of the stool by reducing surface tension at the oil-water interface of the stool.

Thus, water penetrates the stool and softens it. In a clinical study soon to be reported, it was found that DSS in 50 mg. doses produces a soft, maleable stool in approximately seven hours after ingestion. Therefore, for stool softening purposes, this quantity of DSS appeared to be the most logical amount to use. General clinical experience by us and others has shown that larger quantities of the wetting agents have not materially changed the stool consistency.

Since dryness of the stool is one of the most basic causes of constipation, the combination of a wetting agent with clinically proven Senna principles seemed a most logical one. If data on hand were true, this combination would produce a softened fecal mass and be followed by gentle neuroperistalsis to move the malleable mass to the rectum.

Actually, constipation can be divided into four groups: 1. Functional, 2. Dietary deficiency, 3. Secondary to anatomical defects, and 4. Drug induced.

To obtain the following results, the so-called "double blind" technic was used. Briefly it was as follows:

Capsules containing the combined drugs were made up to appear like a similar group of capsules, containing a placebo. Actually, the floor nurses and charge nurses were unable to differentiate between the two, except that one bottle contained "A" capsules and a similar bottle contained "B" capsules. In all patients except the immediate postoperative group, the nurses were instructed to alternate the two groups of drugs to the same patients and record their impressions. Inevitably, the placebo capsules were reported as ineffective, except in five patients, in whom actual so-called effect was thought to be a carry-over from previous ingestion of Senokaps.

The average capsule dose used was one capsule per day, given at bedtime. These capsules contained 225 mg. of the standardized Senna pod principles and 50 mg. of Dioctyl Sodium Sulfosuccinate.

Following major surgery, most postoperative enemas were eliminated, and there were no reported cases of fecal impaction. It is a well known fact that postoperative patients, especially those in the older age groups, suffer from constipation and abdominal distention secondary to atony, of not only intestinal musculature, but also loss of tone associated with pain of the anterior abdominal wall, which plays an important role in the act of defecation. Of the total number of hospitalized patients, this group of 40 comprised the largest single number.

In the orthopedic patients, Product "S" was found to be of special value in the older age group with fractured hips.

To this group of 100 hospitalized patients, 35 postoperative hemorrhoidectomy patients were maintained on Senokap from the first postoperative day. In this specialized group, fecal impaction was avoided and in only one patient was it necessary to resort to an enema. Only one capsule per day was ordered, except in those patients who complained of constipation prior to surgery. In this latter group, two capsules per day were found to be sufficient.

A group of 15 prenatal patients were treated by some of my colleagues with this drug. In like fashion, it was effective in the postpartum group, especially following perineal repair and the presence of edema.

Seventy-five patients were easily maintained on one capsule per day. Nineteen patients required two capsules per day, while six patients required only one capsule every other day.

In Table I can be seen the type of cases studied:

TABLE I

Number of Patients	Fractures	Surgery	Maternity	Medical	Chronic Constipation	Pre-natal	Average Age
Males	9	12		14	2		34.2
Females	3	28	21	6	1	4	27.3
Total	12	40	21	20	3	4	100 pts.

SUMMARY

1. There has been presented a study of 100 hospitalized patients treated for constipation with standardized senna principle with a wetting agent.

2. The average dose was one capsule per day.

3. No untoward side-effects were noted using this combined drug.

4. It can be used as a mild laxative for children.

5. In an additional group of 35 patients who had undergone hemorrhoidectomy, Senokap supplemented routine enemas postoperatively.

6. It is suggested that Senokap is extremely beneficial in the case of geriatric patients.

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POSTGASTRECTOMY COMPLICATIONS

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An analysis of surgical procedures has an inestimable value when it teaches us methods which improve our technic or enables us to avoid certain complications which eradicate or diminish postoperative morbidity. A purposeful study of 100 gastrectomies performed by one surgeon compared to 100 gastrectomies performed by 14 different surgeons indicates that less complications resulted in the series treated by one surgeon. This finding would argue for a surgical team equipped and trained to do the majority of gastric procedures. Since this is a practical impossibility, we must, of necessity, concern ourselves with postgastrectomy complications and their prevention and/or treatment. Unfortunately the record shows that most complications occurred when a gastrectomy was performed by the occasional operator who perhaps would do one or two gastrectomies per year.

A critical study of 200 patients who were subjected to gastrectomy by different surgeons unfolded the following complications on the postoperative day indicated.

First postoperative day

1. Bleeding (internal or superficial).
2. Traumatic pancreatitis.
3. Postoperative shock.
4. Acute gastric dilatation.

Second postoperative day

1. Pulmonary atelectasis (future abscess).
2. Wound dehiscence (incipient stage).

Third and fourth days

1. Duodenal "blow-out" (future subphrenic abscess).
2. Leakage at anastomosis.
3. Jejunal obstruction (efferent loop).
4. Esophagitis (intubation irritation).

Fifth and sixth days

1. Peritonitis.
2. Wound infection and/or disruption.

Seventh day

1. Small bowel obstruction (resect omentum).
2. Postgastrectomy syndrome.
3. Edema of stoma (hypoproteinemia).
4. Gastrojejunocolic fistula.

Delayed complications any time after the seventh day

1. Diarrheas.
   (a) Long loop jejunal anastomosis.
   (b) Gastrojejunocolic fistula.
   (c) Gastrocolic fistula (surgical error).
2. Marginal ulcer.
3. Gastritis.
4. Hematemesis (gastritis or marginal ulcer).
5. Postvagotomy stomach.
6. Thrombophlebitis and/or phlebothrombosis.

The above mentioned complications were found in 30 patients of the 200 studied (6.6 per cent). It is of interest to note that the least number of complications occurred in patients upon whom a Hoffmeister-Finsterer *(oralis partialis)* procedure was performed and that the majority of disturbances were in patients with Polya *(oralis totalis)* anastomosis. The series of 100 patients operated upon by one surgeon exclusively demonstrated only one serious complication.

First Postoperative Day Complications

On the first postoperative day following gastric surgery, one of the most serious complications is the occurrence of bleeding. This may be either superficial in the operative wound or may be internal or intraabdominal at the various operative sites. The sites of special danger are at the anastomosis or at the duodenal stump. Fortunately, this complication is not a frequent one. When it does occur, however, especially at the anastomosis site, bright red blood is either vomited or aspirated from the indwelling tube, which is in the patient's stomach.

If the bleeding is severe, operation may be imperative for the control of hemorrhage. The usual course of events, however, is for the bleeding to cease of its own accord.

Within the first 24 hours following gastric surgery, the patient may develop a traumatic pancreatitis. This complication arises from the fact that trauma to the pancreas has resulted from surgical manipulation of the pancreas or else dissection in the vicinity of the pancreatic head or the removal of a posterior penetrating duodenal ulcer has resulted in localized pancreatic necrosis. The spread of this localized pancreatitis can result in marginal or diffused pancreatitis. If the pathological process is of sufficient severity, then the symptom-complex of pancreatitis results. The cardinal picture of traumatic pancreatitis is that of diffuse abdominal pain associated with shock.

Shock resulting from pancreatitis must be differentiated from simple postoperative shock which is another complication that may result from gastric surgery within the first 24 hours following operation. It has been our experience that postoperative shock following gastric surgery can occur more readily in patients who have exhibited a preoperative hypoproteinemia. Therefore, the correction of a preexisting hypoproteinemia is the most satisfactory method of preventing postoperative shock.

During the first 24 hours following surgery, it is possible for the patient to develop an acute gastric dilatation. This too is a not too frequently encountered complication. When it does occur, however, it is most distressing to the patient and is wrought with the danger of leakage at the anastomosis site. Leakage of this type inevitably results in peritonitis. The diagnosis of acute gastric dilatation is readily made by a scout film x-ray of the abdomen.

Second Postoperative Day

The sudden rise in temperature of a patient following major surgery on the second postoperative day usually indicates some type of complication developing in the lungs. The most common complication is pulmonary atelectasis. This atelectasis may be either limited to a bronchopulmonary segment, a lobule, or a lobe depending upon the area of the bronchial tree that is occluded. It may be necessary to bronchoscope some patients who have moderate to massive atelectasis. It is well to remember that following an episode of atelectasis, it is quite frequent for the patient to develop the further complication of a pulmonary abscess.

The beginning of another dangerous complication may occur on the second postoperative day. This complication is a wound dehiscence. The only sign that may be present at this time may be a serious pink stain on the abdominal dressing. The persistence of this type of drainage strongly suggests that a wound disruption is in the offering.

Third and Fourth Days

During the third and fourth postoperative days, the danger of a duodenal "blow-out" is ever present. If the duodenum itself does not completely "blow-out", the danger of a slow leakage or a pin-point breakthrough may occur. Depending upon the amount of leakage from the duodenal stump, the symptom-complex will vary. A true massive breakdown at the duodenal stump can produce the signs and symptoms similar to a perforated ulcer. If there is only a small leakage, the abdominal findings will suggest a localized peritonitis. A pinpoint breakthrough may manifest itself later as a subphrenic abscess. From this observation, it can be deducted that the complicating picture of a subphrenic abscess may occur at any time from the third postoperative day onward. It is well, therefore, to bear in mind the ever present possibility that a subphrenic abscess may be developing when the patient has a fever the exact site of which is not readily demonstrable. A leakage at the anastomosis site will produce the same type of complication and clinical picture as described for duodenal leakage and "blow-out".

A complication directly attributed to the surgical procedure is jejunal obstruction. It usually occurs in the efferent loop. The obstruction occurs at this time because the peristalsis increases due to the fact that the patient is commencing to ingest liquids and some solid food. The hypermotility in the efferent loop can result in the twisting of a jejunal segment. This complication occurs more easily in patients who have a large pendulous omentum. For this reason, it has been our practice to resect the omentum routinely in those patients who have this suspicious type of omentum.

The esophagitis may occur on the third and fourth days following gastrectomy because of the indwelling tube. Formerly, it was a common practice to allow the tube to remain in the patient for many days. It is our practice to remove the tube as soon as bile drainage occurs. This type of drainage is usually seen within 36 or 48 hours following surgery.

Fifth and Sixth Days

The clinical signs of peritonitis may develop any time following surgery as previously mentioned. On the fifth and sixth days, however, the complicating signs of peritonitis become more recognizable. The peritonitis may be due to any of the previously mentioned causes or from the breakdown of a gangrenous patch in the stomach or the jejunum.

At about this same time following surgery a wound infection may manifest itself or the wound disruption will be in evidence. Wound disruption on some occasions demands taking a patient to the operating room for a secondary closure of the incision.

Seventh Postoperative Day

A small bowel obstruction that had its beginning several days previously may present a classical picture on or about the seventh postoperative day. The patient's abdomen becomes markedly distended with or without vomiting and he is clinically quite ill. A flat plate x-ray of the abdomen will identify the underlying complication. Surgical intervention may be necessary in some cases. It is interesting to note that on or about the seventh postoperative day, it is possible to detect the earliest signs of postgastrectomy syndrome. Although the clinical picture is not very defined, the patient may complain of nausea with or without vomiting, sweating, and cardiac palpitation following the ingestion of food. As time goes on, this syndrome will manifest itself more accurately. The exact time following the ingestion of food with the production of the above mentioned complaints is about 10 to 15 minutes. It can, of course, delay its classical picture anywhere from two months to four years after gastric resection. Many thoughts have been presented as to the cause for this dumping syndrome. Distention of the jejunum has been indicted as the cause for this sequela. Other authorities have stated that contraction of the jejunum following the ingestion of food produces this complication. Hypermotility of the jejunum may also be a factor in the production of this distress because the use of Banthine and similar drugs which are known to diminish intestinal hypermotility have been useful in the treatment of the postgastrectomy syndrome. The jejunal hypermotility in the postprandial period accounts for the nausea, vomiting and diarrhea that occurs in the syndrome. The jejunal hypermotility, however, probably is not responsible for the vasomotor symptoms.

Although the postgastrectomized patient frequently has impaired fat absorption and often sustains a moderate loss of fat in the stools, a greater threat to adequate nutrition is the decreased food intake which characterizes most of these patients. This decreased caloric intake may be related to the accompanying postcibal symptoms. The most common complaint is epigastric discomfort, varying from a full feeling to nausea, vomiting, and severe pain. A minority of patients manifest, in addition, vasomotor symptoms which vary in severity from mild to severe. These include weakness, fainting, sweating, flushing of face, palpitations, and drowsiness. The epigastric pain or feeling of fullness, vomiting, and vasomotor symptoms constitute the early postgastrectomy syndrome, although not all elements are present in each case. Frequently electrocardiographic changes accompany the vasomotor symptoms. These are characteristically lowering or flattening of the T-waves and depression of the S-T segment.

The cause of the early postgastrectomy syndrome has been widely discussed and many theories proposed. The most generally accepted theory has been that the gastric contents empty very rapidly into the jejunum, causing distention of the efferent loop. Such distention may explain the feeling of fullness and pain, but the mechanism of the vasomotor symptoms has not been clear.

The demonstration that hypertonic solutions of sugar are particularly likely to result in such vasomotor symptoms suggested that the vasomotor symptoms occurred when distention of the jejunum resulted from mobilization of large amounts of fluid through the blood-intestinal barrier as a result of the osmotically active carbohydrate. Recent investigations have demonstrated that the autonomic discharge is probably not a result of local jejunal or gastric factors but rather is due to an acute decrease in circulating blood volume which occurs when plasma water shifts into the intestinal lumen. A decrease in serum potassium concentration has been suggested as a cause for the electrocardiographic changes and the symptomatology in this syndrome. The serum potassium changes, however, do not occur coincidentally with the vasomotor symptoms or electrocardiograph changes, and such electrocardiographic changes have been noticed coincidentally with the observed decrease in blood volume after intrajejunal administration of hypertonic saline or carbohydrate.

The "late" postgastrectomy symptoms usually consist of weakness, dizziness, and palpitation, occurring one and one-half to three hours after a meal. These may be indistinguishable from the early vasomotor symptoms except for the time of occurrence. These "late" symptoms are usually mild and require little therapy. Hypoglycemia is thought to be the mechanism for the production of symptoms. It has been pointed out that the characteristic oral glucose tolerance curve shows a persistence of the postprandial hypoglycemia longer than in normal persons. This type of response may also be demonstrated by means of an intravenous glucose tolerance test.

In spite of the apparently sound physiologic basis for the early and late postgastrectomy symptoms, the fact remains that not all patients with similar operative results manifest these symptoms. Opinions persist that the emotional make-up of the patient determines to a large extent whether he or she will develop the vasomotor component of either the early or late syndrome. Some evidence exists that the type of gastrectomy determines the occurrence and severity of the postgastrectomy symptoms and nutritional problems. The Billroth I operation is reported to be accompanied by a smaller incidence of troublesome sequela than the Billroth II, although the differences in occurrence of dumping are slight. In one series of Billroth II operations, the amount of stomach removed was directly correlated with incidence and severity of symptoms. In any choice of operation, however, other factors besides the occurrence of the postgastrectomy syndrome must be considered.

Postgastrectomy symptoms may be abolished or very much improved by the application of certain dietary principles. These include the administration of multiple small meals, the insistence on rather dry meals, and a high-fat, high-protein diet with minimum amount of easily hydrolyzed carbohydrate. This latter restriction has been quite successful in controlling symptoms and is based on sound physiology.

Following gastric surgery, the patient has a great facility for developing hypoproteinemia. This results from the fact that the patient, prior to surgery, either has this existing condition or is on the borderline of developing it. Following surgery, limitation of the diet further accentuates the possible threat to the development of hypoproteinemia. Thus it is that the lowered protein content of the blood can result in an edema at the stomal site. When this occurs, the patient presents a picture of gastric obstruction. This includes vomiting, gastric distress, etc. This state is easily corrected by the administration of proteins, especially amino acids. This same complication of stomal edema can have a delayed manifestation on or about the fourteenth postoperative day.

Another serious complication following gastric surgery is gastrojejunocolic fistula. The incipient stages of this complication may commence on the seventh postoperative day. It may occur, however, at any time following surgery. The characteristic finding in a fistula of this type is the onset of diarrhea immediately following the ingestion of food. The diarrheal contents are undigested food particles recently ingested. It is known that this complication can develop months and even years after surgery. It is most commonly seen in those patients who have had an anterior procedure.

Delayed Complications Anytime After the Seventh Day

As discussed previously, the onset of diarrhea following gastric surgery may indicate gastrojejunocolic fistula. It may also indicate a gastrocolic fistula which may or may not be attributed to a surgical error. There has been one instance in which the stomach has been anastomosed to the colon. This error is equivalent to the complication of a gastrocolic fistula. Diarrheas may also occur if an anastomosis is performed between the stomach in a loop of the jejunum which is taken too far from the ligament of Treitz. This too is attributed to a surgical error in judgment.

Marginal ulcer is a postoperative complication that may present itself at any time following surgery. It is the development of a new ulcer at the site of previous surgery (stomal ulcer). The symptoms produced by marginal ulcer are similar to those of a peptic ulcer. In brief, a patient who complains of the same type of pain after gastrectomy that he had before gastrectomy, indicates that a marginal ulcer is present or is in the process of developing.

Most patients with duodenal or gastric ulcers have an associated gastritis. Following surgery the gastritis remains in the gastric residuum. It is for this reason that the postgastrectomy patient must adhere to a strict diet for a variable period of time ranging from six to eighteen months. It is highly probable that dietary indiscretions may accentuate or make more severe a pre-existing gastritis. This gastritis can be so diffuse that hemorrhage may result.

Hematemesis following gastrectomy can indicate, therefore, one of two things. As previously mentioned, gastritis may be an underlying cause for bleed-

ing. A second complication producing hematemesis is marginal ulcer, which has been previously mentioned. These two complications causing bleeding may occur any time after surgery. By any time is meant a period of months or years.

The postvagotomy stomach is not truly a complication of gastric surgery because following a vagotomy it is anticipated that the normal physiology of the stomach will be disturbed. If a vagotomy is contemplated, the patient should be advised of the possible change in gastric physiology and should be apprised of the fact that certain disturbing symptoms including the possibility of loss of appetite may result.

Thrombophlebitis and/or phlebothrombosis are complications which are not indigenous to gastric surgery but may occur following other surgical procedures. It is merely included here because this complication occurred in one patient reported in this series.

Conclusions

A purposeful study of 200 gastrectomy patients was made. The objective of this study was to bring to light, evaluate and study from a critical point of view postoperative complications. These complications are categorized according to the postoperative day on which they occurred or may occur. The most serious complications directly attributed to the surgical procedure of gastrectomy have been emphasized particularly. It has been found that the surgeon who performs many gastrectomies has the least complications. Contrariwise, the surgeon who occasionally performs a gastrectomy has the most complications. These findings argue for the beneficial effects of gastric surgery to the patient in the hands of the seasoned gastric surgeon.

DIVERTICULOSIS OF A MECKEL'S DIVERTICULUM

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Introduction

Diverticulosis of a Meckel's diverticulum, as far as we can determine has not been reported in the literature to date. Because of the extreme rarity of this type of diverticulum we feel that it deserves publication.

Case Report

Mr. J. S., a 39-year old, white male, was admitted to the surgical service (J.T.K.) of the Lourdes Hospital, Binghamton, N. Y. with the chief complaint of pain in the right side of the abdomen, of approximately three days' duration. The pain was not related to meals and there was no nausea or vomiting, but there was associated anorexia. The patient's bowels moved once on the day of admission and the stool was dark and rather loose but without colic.

Physical examination revealed a well developed and well nourished white male in no apparent acute distress. Weight was 150 pounds, and the general examination was within normal limits except for local abdominal findings. There was rather marked tenderness on the right side about 2 inches above McBurney's point with some muscle spasm.

The laboratory findings revealed a white blood count of 12,750 with 77 per cent polys, (67 per cent filaments and 10 per cent nonfilaments) 18 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophiles. The red blood count, color index and urinalysis including microscopic were not remarkable. The recumbent and upright x-ray films of the abdomen were interpreted as being normal.

A surgical consultation was obtained and it was also the impression of the consultant that the patient had appendicitis and laparotomy would be advisable. The patient was subsequently taken to surgery on the day of admission and through a right lower rectus incision the abdomen was explored. The appendix was not found to be acutely inflamed. A search was made for a Meckel's diverticulum which was found. The diverticulum was interesting in that it was shaped like a fallopian tube. It was resected and the appendix excised. Postoperatively the patient developed an ileus which was relieved by gastric tube and suction. All sutures were removed and patient was discharged on the eighth postoperative day.

The gross pathological examination described the second specimen (diverticulum) as consisting of a pouch-like structure measuring about 3.5 cm. in length and about 2.5 cm. in diameter. At its blind end, a number of secondary diverticuli were present. The entire mucous membrane was congested and the wall appeared to be edematous and congested. Sections of the diverticulum revealed considerable reduplication of the mucosa and small islands of mucosa in the wall. There was mild chronic inflammatory reaction. The diagnosis was diverticula with chronic inflammation. The first specimen (appendix) grossly revealed the distal half to be fibrosed and obliterated. Sections of the appendix showed complete obliteration of the lumen with dense fibrous and adipose tissue. The diagnosis was fibrosed appendix.

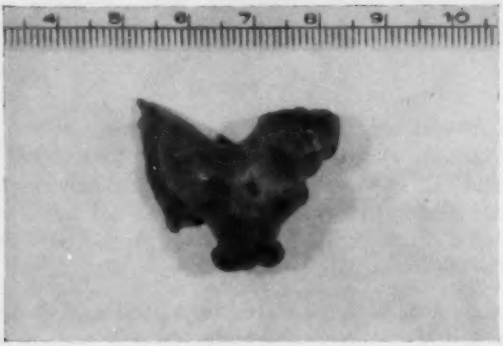

Fig. 1

Comment

The Meckel's diverticulum in this case was most unusual as evidenced by the illustration (Fig. 1). There were four secondary diverticula measuring up to and over 1 cm. in length and approximately five tertiary diverticula measuring up to 3 mm. in length.

Wilson[3] was the first to report a diverticulum of a Meckel's. His diverticulum was 3 mm. in size and located near the free-end of the Meckel's. It occurred in a male and as far as he could determine in reviewing the literature, it was the first one ever reported.

Gillette and Zoltowski[2] reported a case of an accessory distal diverticulum of a Meckel's. Theirs was approximately 8 mm. in length and 5 mm. in diameter and located at the distal end of the Meckel's. It occurred in a female and as far as could be determined was the second case of a diverticulum of a Meckel's ever reported.

Callander[1] in his book "Surgical Anatomy" (second edition) makes mention of this condition. In Figure 369, in the text, there is an ileal diverticulum (of

Meckel's) illustrated and there are numerous secondary diverticula depicted which are labelled pseudodiverticula. There was no discussion, however, of this condition in the book.

In the first two cases reported there was a single accessory or secondary diverticulum, however, in this instance there were numerous secondary and even tertiary diverticula. Whether these secondary and tertiary diverticula should be called diverticula or pseudodiverticula and whether they are congenital or acquired may create some discussion. We believe that these diverticula are congenital or true diverticula both grossly and microscopically.

Perhaps these terms true (congenital) and false (pseudodiverticulum or acquired) are not the appropriate terms to be used in these cases. In order to clarify the terminology one must differentiate between Meckel's diverticulum which is congenital and those diverticula encountered as in the large intestine many of which are considered acquired. Meckel's diverticulum is congenital and it has a continuation of the small intestinal mucous membrane which carries with it the two layers of the muscular coat of the intestine. In the case of diverticula of the sigmoid for example, the mucous membrane is evaginated through a weakness in the muscular coat and is covered only with serosal connective tissue layer. There is no muscular coat taking part in the wall of these diverticula. In the case reported by Gillette and Zoltowski, the fact was mentioned that secondary diverticula of a Meckel's may be acquired or congenital, however, we are more of the opinion now that this accessory or secondary and tertiary diverticula of Meckel's were also of congenital origin since they have two muscular layers accompanying the mucous membrane.

Summary

1. A case of diverticulosis of a Meckel's diverticulum has been reported.

2. This is the first case of its kind ever reported in the literature as far as we can determine.

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President's Message

Gastroscopy

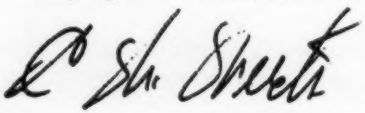
One of the adjunct meetings of the recent World Congress of Gastroenterology held in Washington, D. C., was that of the American Gastroscopic Society. Approximately half of the 23 speakers were from abroad; England, France, Germany, Japan and Australia were represented, and it is of interest to note how a similar trend of broadening experience is taking place on a world-wide basis.

Special attention was given to gastroscopic biopsy, gastroscopic photography, the development of the fiberscope and the development of color television through the gastroscope. The majority of the discussants appeared to favor the opinion that the ultimate diagnosis of gastritis rests upon biopsy. Histologically there appears to be a superficial and atrophic but not hypertrophic form of gastritis. When atrophy is seen gastroscopically it is always confirmed histologically but atrophic gastritis may be diagnosed by biopsy when not seen grossly. Some data still supports the theory that atrophy is the end form of gastritis and perhaps a stage of premalignancy of the stomach.

Dr. Tasaka and his colleagues from Tokyo, Drs. Debray and Housset of Paris and Nelson from Houston have all been able to take excellent gastroscopic colored pictures. Although each of the technics employed varies from the others all are sufficiently simple and practical to permit routine use if desired.

Colored television which will give a screen-sized view of the interior of the stomach is in the developmental stage. Research in this field is being carried out at the Walter Reed Army Medical Center in conjunction with RCA and M.I.T. and a report on their work promises success in the near future.

One of the most radical changes in gastroscopic construction is the so-called fiberscope. Instead of lenses, long strands of finely drawn glass are so arranged as to conduct both light and an image. Images of fair quality can now be obtained through one of these instruments but it is insufficient for practical purposes. Further work, it was stated, will certainly permit successful use of this type of instrument. The great advantage, of course, will be a degree of flexibility equal to a soft rubber tube.



NEW ORLEANS CALLING

PLEASE COME TO NEW ORLEANS! AND WHY!

I think this description of my sophisticated old town can't be improved on—"La Nouvelle Orleans" is a Southern Belle, who never completely threw away her crinoline. Best known for hot trumpet jazz, crab gumbo, *pompano en papillot* and black midnight coffee. New Orleans is a waterfront hussy, who survived plague, fire, flood, Indian wars, six changes of government and the worst political racketeers in living memory, to emerge as the South's largest city, a new industrial frontier and one of the nations' busiest ports. In the shadow of huge oil company skyscrapers are ninety blocks of neon-lit old world French Quarter, a mecca for writers, artists, socialites and Bohemians.

See—a port serving a huge chunk of territory from Cincinnati to Denver; weird chemical plants flank the snaking Mississippi River, while half a mile away street artists work at easels among lacy grilled balconies, gabled roofs, mysterious alleyways and crumbling vine-clad walls of the Vieux Carré.

New Orleans presents a unique combination of Creole traditions and customs, side-by-side with vigorous modern American progress.

New Orleans is gay—not morbid and sad—gay at night Blue Room, Swan Room, Safari Room, for the higher things in night life—but more interesting and naughty are the aptly named spots in Vieux Carré: Sho-bar, Famous Door, Prima's 500 Club, etc., etc., etc.

Dixieland jazz, where it was born—
As one New Orleans inhabitant reported with pride—

"They say New Orleans, she is ze Paree of ze New World
"But they are wrong—
"Paree, she is ze New Orleans of ze Old World—
"New Orleans, Ah, ma fran, she is—
"New Orleans—There is no other like her—
"Let's see if you don't agree—"

Louis Ochs, Jr.
Chairman
Program Committee

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In Memoriam

We record with profound sorrow the passing of The Rt. Hon. Lord Webb-Johnson, London, England, Honorary Fellow of the American College of Gastroenterology.

Lord Webb-Johnson participated in the first Course in Postgraduate Gastroenterology of the College held in Boston, Mass., October 1949 and received his Honorary Fellowship in 1950. He was a past-president of the Royal College of Physicians of England and at one time physician-in-chief to the King of England.

We extend our deepest sympathies to the members of the bereaved family.

ABSTRACTS FOR GASTROENTEROLOGISTS

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GASTROINTESTINAL TRACT

GLOSSITIS: N. B. Jaffe. Med. Times 85:383 (Apr.), 1957.

The tongue has long been neglected as an organ of diagnostic criteria, but if studied carefully will give an insight to or a clue of many conditions affecting the body.

For example, a dry, furred tongue is present in fevers and dyspepsia, in hepatitis the anterior portion is furred; adrenocortical dysfunction lends pigmented spots to the surface as do many medications.

In deficiency diseases atrophy of the papillae occurs. In chronic lues we have leukoplakia with cobble-stone roughness, this often becoming malignant. The hyperkeratoses may be associated with excessive smoking, use of spices, condiments or alcohol, carious teeth or ill-fitting dentures. The outlook in these cases is ominous.

Blood dyscrasias produce lingual hemorrhages, pernicious anemia and sprue often give deepseated lingual pain.

In hemiplegia the protruded tongue deviates from the midline; in dementia paralytica, fevers and alcohol, it is tremulous; in bulbar paralysis it fibrillates.

A better understanding and keener observation of the tongue will lead to more exact and quicker diagnoses in many perplexing conditions.

J. EDWARD BROWN

ESOPHAGUS

CHANGING CONCEPTS IN THE STRUCTURE, FUNCTION AND DISEASE OF THE LOWER ESOPHAGUS: David M. Gould and Howard J. Barnhard. Am. J. M. Sc. 233:581-595 (May), 1957.

This article is from the Department of Radiology of the University of Arkansas Medical Center and discusses primarily questions of interest in regard to the structure and function of the lower esophagus. For instance, the discussion centers around just where the esophagus ends and the stomach begins. The closure mechanism of the lower esophagus is detailed. Hiatal hernia and peptic esophagitis, chalasia and achalasia are described. Three types of ulcerative disease of the esophagus are outlined. The article primarily briefly reviews the literature concerning the subjects listed.

BERNARD FARFEL

TRAUMATIC PERFORATION OF THE ESOPHAGUS CAUSED BY SELF-CATHETERIZATION WITH HEAVY ELECTRIC WIRE: Edward S. Brewster, Am. J. Surg. 93:1021 (June), 1957.

Perforation of the esophagus by self-instrumentation is a most unusual accident. No similar case has been noted in medical literature.

Before the advent of sulfa drugs and antibiotics, perforation of the esophagus was considered fatal in practically all cases. They are usually caused by: 1. Endoscopic procedures, 2. ingestion of foreign bodies and their removal, 3. taking of biopsy specimens, 4. dilation of strictures. The article discusses a case report and the treatment.

CARL J. DEPRIZIO

STOMACH

NUTRITIONAL DEFICIENCIES IN GASTROCOLIC FISTULA: A. M. Connell. Scottish M. J. 2:162 (Apr.), 1957.

A case of gastrocolic fistula subsequent to gastroenterostomy is discussed. The case presents in a striking manner the severe deficiencies which may follow. The plasma proteins were reduced to 50 per cent of normal, well below the edema level, but with no change in the A/G ratio. A calcium deficiency was present and was indicated by signs of muscular hyperexcitability. Clinical signs and blood levels indicated severe vitamin deficiencies of ascorbic acid and members of the B-complex.

Preoperatively, the patient received whole blood transfusions, a high protein, high vitamin diet and injections of Vitamin B-complex and K. The diarrhea was controlled by hexamethonium, and the edema removed by injections of mersalyl to promote diuresis. Chlortetracycline was used to control infection before, during and after surgery.

ARNOLD L. BERGER

GASTRIC SURGERY IN ELDERLY PATIENTS: Stanley O. Hoerr. Cleveland Clin. Quart. 24:116 (Apr.), 1957.

In this article the author reports his results on abdominal surgery in elderly patients. This age group (above 60 years) naturally has a comparatively high incidence of postoperative complications involving the cardiovascular and respiratory systems and the urinary tract. Likewise the immediate in-hospital mortality after operations for advanced malignancies is quite high. Therefore, no operation should be performed for either hopelessly advanced cancer or for very unfavorably located malignancies, which give only minimal symptoms. Nevertheless justification for operation is to be found in the fact that some elderly patients may have curable lesions. The history of a 79-year old patient with a large antral cancer is given. This patient was still living 5 years after radical surgery.

The author gives pictorial statistics on the results of operations for gastric and duodenal ulcers and other nonmalignant diseases.

The importance of pre- and postoperative care is stressed. Skillful management of anesthesia is of utmost importance. With proper management and careful selection abdominal operations on elderly patients are reasonably safe.

H. J. JOSEPH

DEGASTROENTEROSTOMY: Joseph E. Bellas. J. Internat. Coll. Surgeons. 27: (May), 1957.

The author reports two cases. The details of degastroenterostomy and of the Pfeiffer multistage method for gastrojejunocolic fistula are described. Degastroenterostomy the removal of a gastroenterostomy, is an important part in a procedure seeking to cure a malfunctioning anastomatic stoma. It is also important in caring for a secon-

dary peptic ulcer occurring at or about the stoma. The author claims this operation would help a gastrojejunocolic fistula.

In discussing malfunction of a gastroenterostomy, Bellas includes: a. vicious circle, b. a contracted stoma with gastric retention and c. a wide open stoma without vicious circle complications, without secondary peptic ulcer but with gastric retention.

ABRAHAM BERNSTEIN

THE ROENTGEN DEMONSTRATION OF DUODENAL ULCER: Edward R. Heitzman, Jr. U. S. Armed Forces M. J. 8:644 (May), 1957.

The increasing incidence of duodenal ulcers and the necessity of roentgen differentiation from stomach ulcerations are again reviewed. Since a gastroenterologist or a roentgenologist is not always readily available the author briefly but succinctly summarizes the primary and secondary signs of duodenal ulcers including less commonly used maneuvers such as air contrast spot films and the posterior oblique views to demonstrate posterior wall craters.

Regardless of background very few physicians will not find this article worth reading and useful. And all will certainly appreciate the author's last paragraphs emphasizing the difficulty in evaluating the complete healing of duodenal ulcers by roentgen follow-up examinations alone.

A. M. SUSINNO

THE ROLE OF SURGERY IN BLEEDING PEPTIC ULCER: L. Kraeer Ferguson, Donald R. Cooper and Leroy H. Stahlgren. Am. Pract. & Digest Treat. 8:726 (May), 1957.

It is difficult to determine whether to treat a bleeding peptic ulcer medically or surgically, so several approaches to this problem have been advocated;

1. All acutely bleeding peptic ulcer cases get blood replacement and early gastric surgery. Here diagnostic errors were 10.2 per cent and mortality 8 per cent.

2. In massive hemorrhage and history of chronic peptic ulcer, partial gastrectomy immediately. Here mortality was 7.5 per cent.

3. Patients treated conservatively until further treatment proved hazardous. Here 22.4 per cent were operated on with a mortality of 8 per cent.

4. Selective intervention in treatment of peptic ulcer;

   a. Choose those patients who may die from hemorrhage with conservative treatment.
   b. Make choice early in the course of bleeding.
   c. Prepare patient and operate within 48 hours to control bleeding.

Factors influencing choice of patients who may die from hemorrhage from conservative treatment:

1. Age—increasing age produces increasing risk. The complications attendant with old age, such as, hypertension, cardiac, cerebral vascular diseases, nephritic, liver diseases, etc. In general under 50 the mortality rate is one-half that over 50.

2. History and site—Bleeding from gastric ulcer, the prognosis is poor and mortality is 22 per cent compared with 10 per cent in duodenal ulcer.

3. Hematemesis or melena—hematemesis suggests bleeding from stomach or duodenum. In hematemesis and melena mortality is 20 per cent, whereas in melena alone the mortality is only 4 per cent.

4. Number of hemorrhages—a first bleeding may be fatal. In patients over 50 with a history of chronic gastric ulcer and hematemesis, do surgery.

5. Factors influencing for or against operation are:

   a. Rate of bleeding.
   b. Duration of bleeding.
   c. Response to transfusion.

6. Early selection of cases for operation —mortality is less 7-10 per cent in those operated on early, compared to 55 per cent where done as a last resort. Operate within 48 hours. Esophageal varices can be excluded by bromsulfalein tests, enlargement of liver or spleen. Appropriate blood studies to exclude blood dyscrasias.

7. Operate even without establishing definite diagnosis for following reasons:

   a. In 85-90 per cent of cases bleeding is due to peptic ulceration.

b. May have bleeding without history of chronic peptic ulcer.
c. Dangerous and impossible to make x-ray studies and may cause:
1) Unwarranted delay in operation.
2) Barium in colon may cause serious intestinal complications.
d. Even in bleeding dyscrasias and esophageal varices bleeding can be controlled by operation.

8. If operation is decided upon, prophylactic measures to be taken are:
a. Sufficient blood should be available.
b. Stomach should be emptied by gastric suction.
c. Intratracheal anesthesia should be used to avoid aspiration of vomitus.

9. At operation several principles should be followed:
a. Control bleeding by attacking bleeding point.
b. Partial gastrectomy is operation of choice.
c. Remove ulcer as part of treatment for bleeding. If it cannot be removed exteriorize or exclude it.
d. If bleeding cannot be found by palpation and inspection 2 methods are available:
1) Wide gastrotomy—this method is unsatisfactory.
2) Blind resection—more adequate and is best, as it removes the acid-bearing portion of the stomach as well as possible areas of bleeding.

LOUIS K. MORGANSTEIN

ACUTE VOLVULUS OF THE STOMACH EMPHASIZING MANAGEMENT HAZARDS: A. A. De Lormier and Loyd Penn. Am. J. Roentgenol. 77:627, 1957.

Incomplete volvulus may occur up to 180 degrees without obstruction or strangulation of the blood supply. Twisting beyond 180 degrees usually results in a complete obstruction with clinical manifestation of an acute abdomen. The differential diagnosis is gastric atony, intestinal obstruction, sigmoid volvulus, cecal volvulus, acute pancreatitis with a selective type of adynamic ileus and a ruptured ulcer. Atypical roentgenological criteria are: a. local massive distention of the upper abdomen; b. frequent visualization of outlines of a hairpin loop with incisura directed toward the right upper quadrant or posteriorly; c. fixation of the loop, regardless of decubitus or Trendelenburg positioning of the patient; d. termination of the ingested barium at the tapered extremity of the esophagus; e. possible evidence of a hiatal circulation or other diaphragmatic herniation; f. accurate graphic evidence of deviation of the spleen anteriorly or inferiorly; g. segmental distention of the loops of the small intestine and of the colon which is evidence of an associated adynamic ileus. The following warnings as to management of an acute volvulus are: the taking of baking soda for relief of gastric distress, importance of over-counteracting and over sedation before releasing tension of a distended viscus, attempts to pass a stomach tube, surgical relief with assistance to pharmacological and food balance requirements.

V. J. GALANTE

INTESTINES

NONSPECIFIC CONDITIONS OF THE LARGE INTESTINE: Eric A. Crook. Proc. Roy. Soc. Med. 50:237 (Apr.), 1957.

The three nonspecific conditions referred to in this article are ulcerative colitis, regional enteritis and lymphogranuloma venereum. Before 1875, any long-standing or recurrent diarrhea was considered idiopathic or ulcerative colitis. Many diseases such as dysentery, typhoid, tuberculous ulcerations, regional enteritis and enterocolitis, as well as lymphogranuloma have since been shown to be separate entities. It is possible that even now what we consider ulcerative colitis still comprises several different diseases.

The authors discuss the similarities and dissimilarities of the three nonspecific conditions of the colon and terminal ileum as

regards to their etiology, incidence, course the three diseases follow, the pathologic changes in each, and their response to treatment.

In conclusion, they feel that "the similarity of the early stages of all three diseases suggest that they may be one and the same disease. The special features in each may be explained by the local difference in the region of bowel involved, modified by idiosyncrasies of the patient and differences in race and climate."

A. J. Brenner

DIAGNOSIS AND MANAGEMENT OF ANORECTAL PAIN: Herman Miller. Med. Times 85:359 (Apr.), 1957.

This simple article brings no new observations to our voluminous literature. The author restates some of the anatomy and stresses the pain factor in proctologic diseases, which is aggravated in some instances by overtreatment. This is especially true when the "caine" derivatives are used topically. Gentle examination is described, and the necessity of a correct diagnosis and good judgment for adequate treatment is reiterated.

Norman L. Freund

CARCINOMA OF THE CECUM PRODUCING INTUSSUSCEPTION: Leonard K. Stalker, James J. Clements, Fuad A. Mukhtar. J. Internat. Coll. Surgeons 27:428 (Apr.), 1957.

Adult intussusception is not a common occurrence when compared to the frequency with which ileocecal intussusception is reported in infants and children. The case history of a patient recently treated by the author is therefore reported. The case in question is that of adult (65-year old housewife) ileocecal intussusception due to carcinoma of the cecum and complicated by achalasia of the esophagus. It seemed probable that the carcinoma was present for at least a year, its detection having been delayed by the fact that the presenting symptoms were attributed to the achalasia. This patient was subjected to surgery and had an uneventful recovery. The surgery was a radical hemicolectomy followed by a primary ileocolostomy.

Bernard J. Ficarra

VALUED AIDS AND ESSENTIALS IN ANORECTAL SURGERY: Charles Evans Pope. Illinois M. J. 111:234 (May), 1957.

This article presents certain ideas of the author regarding management of the patient undergoing anorectal surgery. Being an article he has necessarily limited it to certain aspects of the field and in doing this is unable to explore fully the factors that are involved. This is understood and must be accepted.

The article points up numerous items which may have slipped the mind of the casual rectal operator. Extensive bibliography is appended.

Paul B. Van Dyke

COLON DUPLEX: William S. Judy, Jr. Northwest Med. 56:586 (May), 1957.

A case of reduplication of the entire colon is added to the literature, making 24 cases in all. These may be divided into simple colon reduplications, which are considered as diverticula, or true twinning of the hind gut, in which instance there is associated genitourinary reduplication.

A 42-year old white married female had a roentgen examination of the colon: Roentgenoscopy showed the barium immediately dividing into separate rectums which joined approximately 2 cm. proximal to the anus. The segments filled simultaneously and were parallel and of equal caliber. Both appeared to function. Colons were joined at the cecum and had a common terminal ileum.

Subsequent clinical examination revealed normal external genitalia and uterus.

Jacob A. Riese

THE MANAGEMENT OF COMMON DIARRHEAS: Robert W. Kelley. Mississippi Valley M. J. 79:154 (May), 1957.

The immediate approach to treating diarrhea will depend on the acuteness of the process. With acute food infections the patient may become quite ill. This severity of illness results because of the fluid and electrolyte loss. Thus the treatment aims primarily at the replacement of fluid and electrolytes. The diarrhea should be controlled as rapidly as possible. If vomiting occurs medication may be administered parenterally. Codein is advocated for such patients. Paregoric is given to those patients who can take it by mouth. Diet is given according to a prescribed routine. Meals should be regularly spaced. In the chronic diarrheas antispasmodics are effective. Often a combination of the antispasmodic with a sedative is most effective. Bismuth in any form is a valuable preparation in most chronic diarrheas. There are multiple chemotherapeutic and antibiotic agents which are effective in combatting specific infections producing diarrhea. In the acute diarrheas there is usually no need for using the sulfa drugs.

BERNARD J. FICARRA

CHRONIC DUODENAL ILEUS: Roscoe C. Giles. Am. J. Surg. 93:824 (May), 1957.

The author states that this a clinicopathologic entity characterized by intermittent delay in the passage of the duodenal contents through the transverse or third part of the duodenum. The condition has many other synonyms, e.g., Wilkie's Syndrome, chronic duodenal stasis, etc. The first case was noted by Boerneus in 1752.

Several explanations have been proposed for this condition. One of these is compression of the 3rd part of the duodenum, where it traverses the spine, by the root of the mesentery of the small intestine which contains the vascular structures, nerves and lymphatics. Bloodgood advanced the idea that prolapse of the cecum pulled on the mesentery of the small intestines and that duodenal obstruction resulted when the last portion of the ileum has a short mesentery. Other theories of the pathogenesis of the condition are noted.

The syndrome may closely simulate biliary colic or peptic ulcer. The clinical diagnosis is usually made by x-ray examination.

If patients do not respond well to medical treatment surgery is inevitable and invariably successful. This consists in performing either a duodenojejunostomy or a gastrojejunostomy, the latter is preferred because it gives consistently better results.

The author reports one case, female age 36, who was operated upon, recovered and well more than two years after surgery.

CARL J. DEPRIZIO

DIAGNOSTIC VALUE OF PARACENTESIS IN THE ACUTE SURGICAL CONDITION OF THE ABDOMEN: Sam D. Weakley, Jr. and Crocker B. Clegg. Am. J. Surg. 93:802 (May), 1957.

The writers believe this simple procedure has received very little recognition and is the least utilized of the presently employed diagnostic aids. The technic is very simple and is described in detail. The patient is usually placed in the lateral decubitus position, tapping the dependent lower quadrant of the abdomen. Local anesthesia may be used if desired although it is not necessary.

When diagnosis is uncertain abdominal paracentesis is indicated to avert unnecessary laparotomy. It has been used in traumatic conditions, inflammatory diseases, and in cases of malignancies. There are no true contraindications and the safeguards are to avoid masses, scars, and the bladder.

Emphasis is placed upon the examination of the aspirated fluid by gross examination and laboratory analysis, consisting of specific gravity, smear, culture, cytology, acid reaction, bile, amylase activity, etc.

Six cases are reported in which abdominal paracentesis was done, the diagnosis established beyond doubt, and the proper surgical and medical treatment timely instituted.

The authors also stress the fact that although positive findings may make the diagnosis, a negative tap should never exclude the possibility of fluid in the abdomen or alter conclusions derived from other clinical evidence.

CARL J. DEPRIZIO

MANAGEMENT OF IMPERFORATE ANUS: Louis Shaffner. North Carolina M. J. 18:202 (May), 1957.

"Initial repair of imperforate anus should not only relieve the obstruction but offer good promise of normal bowel control and function." Hence haste in operation without careful diagnosis of the type of imperforation and associated anomalies is decried. The author claims excellent results in the greater percentage of 41 cases reviewed and states that only 2 of 9 deaths could be attributed to the operation.

The various surgical procedures available are briefly discussed with the conclusion that the "earlier the repair is done, the better chance for normal control and function".

A. M. SUSINNO

APPENDICITIS IN CHILDREN: George W. Paschal, Jr. North Carolina M. J. 18:207 (May), 1957.

The recording of 19 deaths from acute appendicitis in children under age 12 over a 5-year period prompted a review of appendicitis in 358 children. The subject is timeless since the incidence of appendicitis remains unchanged.

The problems of early diagnosis and the unswerving active management when in doubt are again emphasized. The author's philosophy of the roles of antibiotics, anesthesia, electrolytes and "tender surgical care" are presented in view of the zero mortality in his series.

A. M. SUSINNO

AN ASSOCIATION BETWEEN SOCIAL CIRCUMSTANCES AND APPENDICITIS IN YOUNG PEOPLE: J. A. H. Lee. Brit. M. J. 5029:1217 (25 May), 1957.

The mortality from appendicitis is about 20 per cent higher in professional men and managerial workers than it is in unskilled laborers. There is also evidence that the forms of the disease, severe enough to cause hospital admission, are more common among those of higher social and economic status. Statistics are adduced to show that young males are more likely to be operated on for appendicitis and to die of the disease in the Glasgow area than in London. This is an unexpected finding, and the author postulates the existence of a further factor in the causation of appendicitis.

ARNOLD STANTON

LIVER AND BILIARY TRACT

ENLARGEMENT OF THE PAROTID GLAND IN DISEASE OF THE LIVER: Earl N. Rothbell and John J. Duggan, Am. J. Med. 22:367 (March), 1957.

A curious noninflammatory symmetrical enlargement of the parotid gland has been described by several foreign authors. It is associated with malnutrition, beri beri, pellagra, obesity, diabetes mellitus or cachexia. Six similar cases where parotid enlargement was associated with alcoholic cirrhosis or fatty infiltration of the liver were added. The liver disease was established by biopsy. Parotid gland enlargement was also examined by biopsy and showed fatty infiltration without any inflammatory response. Other salivary glands were not involved. Noninflammatory parotid enlargement is a nonspecific sign of various metabolic or nutritional disturbances, but does not indicate any specific disease entity.

H. B. EISENSTADT

CHLORPROMAZINE JAUNDICE, J. Lawrence Werther and Burton I. Korelitz, Am. J. Med. 22:531, (March), 1957.

Twenty-two patients with chlorpromazine jaundice were carefully analyzed. Total dose of the drug taken varied from 10 mg. to 1,260 mg. Systemic symptoms preceding or coincident with the jaundice started on the average of 14 days after the first

dose was taken. Alkaline phosphatase and serum bilirubin were always elevated; serum cholesterol frequently increased, parenchymal liver tests negative. Prognosis was good even if jaundice lasted as long as four months. Six fatalities are reported in the literature, but could be attributed to associated diseases and are probably not caused by thorazine alone. Retreatment after a previous reaction caused accelerated recurrence of jaundice. Liver biopsy revealed eosinophilic periportal cellular infiltration and intracanalicular cholestasis. Similar pictures are seen in arsphenamine, dinotrophenol, toluylenediamine, thiouracil, methyltestosterone, sulfonamide poisoning and viral cholangiolitic hepatitis.

H. B. EISENSTADT

BACTEREMIA DUE TO DIPLOCOCCUS PNEUMONIAE ASSOCIATED WITH DISEASE OF THE BILIARY TRACT: Alexander Schirger, William J. Martin, Carl G. Morlock and Archie H. Baggenstoss, A.M.A. Arch. Int. Med., 90:622, 1957.

Pneumococcic bacteremia is usually associated with pneumonia, bacterial endocarditis usually involving the aortic valve and meningitis; invasion of the biliary tract by these microorganisms is extremely rare. This is explained by the protective action of bile which dissolves the bacilli easily and causes thus their destruction. Two cases of obstructive cholangitis and liver abscesses associated with cancer of the bile duct are reported where these organisms were demonstrated in the blood culture as well as in the liver tissue slides at autopsy. Neufeld who discovered the lysis of pneumococci in bile, encountered occasionally, a strain that was resistant to this action. Such strains may be responsible for pneumococcic involvement of the biliary tract.

H. B. EISENSTADT

HEPATOLENTICULAR DEGENERATION: Gregory S. Ferriss and Spencer Berry, Arch. Int. Med. 90:656, 1957.

This disorder is attributed to an increased absorption of copper from the bowel which, in the absence of its normal carrier ceruloplasmin, is deposited in various tissues, especially in the liver and the brain and is resposible for the damage of these organs. Treatment of Wilson's disease consists of: 1. copper binding chemicals to prevent absorption in the form of oral potassium sulfide, 20 mg. t.i.d. with meals, 2. a high protein diet with supplementary casein hydrolysates to enhance urinary excretion, 3. parenteral administration of chelating agents such as Bal and Versene to withdraw copper from the tissues. A case with severe flapping tremor, Parkinson's rigidity, change of personality and mentality is reported who improved while under this regime. Bal was given in small intramuscular doses (1.7 c.c. daily) for several months. The effect of this therapy was dramatic during the first 3½ months; hereafter further improvement was slow.

H. B. EISENSTADT

HEPATIC INSUFFICIENCY: A REPORT OF THIRTY-TWO NECROPSIED CASES: Maurice Feldman, Am. J. M. Sc. 233:264-267 (March), 1957.

In this case report on hepatic insufficiency, 32 necropsy cases of liver insufficiency are studied. Various intra- and extrahepatic pathology is described and the various blood chemistry values and liver function tests are very briefly reviewed.

BERNARD FARFEL

ANALYSIS OF CAUSES OF DEATH IN LAENNEC'S CIRRHOSIS: George Chase, Cyprien Martel and Renzo Olivetti. Am. J. M. Sc. 233:259-263 (March), 1957.

The authors review 66 cases of Laennec's cirrhosis found amongst male admission to two Veterans Administration Hospitals. The patients vary between the ages of 29 and 67 and each had a history of high and prolonged intake of alcohol. Where other associated etiological factors might be present, the patient was excluded from this series. Hepatic insufficiency was found to be the cause of death in 44 per cent. Hemorrhage

was the cause of 38 per cent, pneumonia in 4.5 per cent and miscellaneous in 13.5 per cent. The authors compare their figures with previous figures going back to 1938 and 1942 and point out that antibiotics have changed the picture in that there is a low incidence of intercurrent infectious diseases as a terminal phase. This has changed the outlook for the patient with cirrhosis. More patients can be expected to die of hepatic insufficiency than of complicating infection. It may be that surgical procedures may reduce the number of deaths caused by bleeding varices.

BERNARD FARFEL

PANCREAS

TUMORS ASSOCIATED WITH HYPOGLYCEMIA—PANCREATIC AND EXTRA-PANCREATIC: M. R. Porter and V. N. Frantz. Am. J. Med. 21:44 (Dec.), 1956.

The authors have reviewed the literature and a group of 56 cases from Columbia-Presbyterian Medical Center have been explored for islet cell tumor. The diagnostic work-up of the hypoglycemic patient must be carried out very carefully in order to justify the frequent necessity for blind resection. If Whipple's clinical triad is rigidly observed in the selection of cases for operation, functional islet cell tumors will be found in the great majority. Forty-seven functional tumors were removed in the authors' group of which there were 33 females and only 14 males. Of this group, 63.8 per cent were benign adenomas. Of the lesions in the authors' series 18.6 per cent were multiple and the operation will fail unless all the adenomas are found and removed. When no adenoma can be palpated after careful exploration, it is their practice to remove all the pancreas to the left of the superior mesenteric vessels. The microscopic entity, hyperplasia of the islets of Langerhans, has never in their adult series been responsible for clinically significant hypoglycemia. In infants and children a correlation between clinically significant hypoglycemia and all abnormal islets of Langerhans is not the same as in adults. Consequently, youngsters with serious degrees of spontaneous unexplained hypoglycemia will be given a trial of ACTH according to the scheme outlined by McQuarrie and will only be explored if major improvement does not occur. A five-year follow-up is not long enough to rule out the possibility of recurrent hypoglycemia due to recurrent or persistent neoplasm. Another case of a large extrapancreatic tumor associated with hypoglycemia is added to the five reported in the literature. The authors were unable to classify it.

JOHN M. MCMAHON

PYLORIC OBSTRUCTION DUE TO PANCREATIC HETEROTOPIA IN A CHILD: D. MacKinnon and F. W. Nash. Brit. M. J. 5010:87 (12 Jan.), 1957.

In discussing the case the author found the incidence to be not uncommon, 15 per cent of cases, and was an incidental finding at necropsy. However, in children pancreatic heterotopia is very rare. Of 471 cases collected in the literature only 46 or 1 per cent occurred in children.

As to the theory of its origin it is supposed to be due to the pancreatic ducts being snared off by the upward and downward growth of the intestines.

LOUIS K. MORGANSTEIN

ACUTE PANCREATITIS FOLLOWING SUBTOTAL GASTRECTOMY: Heinz E. Haffner and Eric G. Ramsey. Missouri Med. 54:29 (Jan.), 1957.

The clinical picture, diagnosis, incidence and suspected etiologic factors of acute pancreatitis following gastric surgery are reviewed. It is probable that the disease results when activated pancreatic secretion is enabled to be excreted into the interstices of the pancreas, this being brought about in a variety of ways. The proximity of the accessory pancreatic duct to the pylorus is emphasized by description of autopsy material.

A report is given of four cases of pan-

creatitis following gastric resection for duodenal ulcer, and preventive measures are discussed. It is suggested that with low-lying ulcers, proximal closure of the duodenum is a safer procedure than difficult duodenal dissection. The incidence of recognizable pancreatitis following subtotal gastrectomy in this series is 2.3 per cent, with a 50 per cent mortality. Even the most energetic treatment is of little avail in a severe postoperative pancreatitis, and it is only by improved methods of prevention that hope may be entertained.

ARNOLD L. BERGER

CHRONIC RELAPSING PANCREATITIS: Martin D. Liemer. Med. Times 85:45 (Jan.), 1957.

The etiology, pathology and the current medical and surgical procedures used for this disease entity are summarized in concise fashion. The controversial features of chronic relapsing pancreatitis, the acute phase included, are stressed since no treatment either medical or surgical is generally accepted.

The fine summarization notwithstanding the author fails to include the intravenous regimen with Lugol's solution reported by Bruger et al for the acute exacerbations of this disabling disease.

A. M. SUSINNO

THE CHALLENGE OF PANCREATITIS: William S. Haubrich. Clin. Med. 4:147 (Feb.), 1957.

Suspect pancreatitis in all acute abdominal conditions. Clinical signs are many and varied. The *sine qua non* is the determination of the serum amylase level. Obtain blood for enzyme determination before administering narcotics for the relief of pain as opiates tend to produce a rise in serum amylase. Never forget that acute *relapsing* pancreatitis may show no significant rise in serum amylase. Arrange for lipase determination as well (as lipase values take longer to become elevated but are more stable and persist longer). Prognostically, a low serum calcium on the 2nd to 5th day is a bad prognostic sign.

A simple scout film of the abdomen may be of considerable aid.

Following an acute attack, evaluation of the liver and biliary tract and patient's habits and mode of life are most important.

IRVIN DEUTSCH

ANEURYSM OCCURRING IN THE PANCREATICODUODENAL ARTERIES TREATED BY EXCISION: Francis P. Catanzaro, Anthony Merlino and Joseph A. Palumbo. New England J. Med. 256:847 (2 May), 1957.

This brief report is the second instance of an aneurysm of the pancreaticoduodenal artery treated by surgical excision. The symptoms and clinical course in this instance resembled an obstructing lesion of the upper gastrointestinal tract.

This lesion is a rarity but the complete relief of symptoms following operation compels the authors to conclude that any significant intraabdominal aneurysm of the smaller vessels be definitively excised since 80 per cent of such reports indicate eventual perforation and hemorrhage from these aneurysms to be fatal.

A. M. SUSINNO

PATHOLOGY AND LABORATORY RESEARCH

THE EFFECT OF RESERPINE UPON BASAL GASTRIC SECRETION IN MAN: Joseph B. Kirsner and Harold Ford. A.M.A. Arch. Int. Med. 99:390, (March), 1957.

Previous experimental and clinical observations have suggested that reserpine may stimulate gastric secretion and gastrointestinal motility in man. Therefore, reserpine was administered at first orally and later intravenously to 24 volunteers during gastric intubation and continuous aspiration of the stomach juice. Oral reserpine in conven-

tional therapeutic doses was found to increase gastric acidity little or not at all, while intravenous injection of the drug in a similar dosage produced a tremendous increase of acid output. This occurred even in vagotomized persons indicating that the parasympathetic activity in Rauwolfia is not responsible for this effect. A pronounced vasodilation with cutaneous flushing, headache, sensation of warmth and hypotension accompanying the gastric stimulation suggested a release of histamine from the intracellular depots as the causative mechanism of the hyperacidity. Increased serotonin liberation must also be considered but is unlikely because urinary 5-hydroxyindoleacetic acid does not increase during the period of stimulation. Intravenous reserpine should not be used in patients with peptic ulcer.

H. B. EISENSTADT

VALUE OF RECTAL BIOPSIES IN THE DIAGNOSIS AND TREATMENT OF SCHISTOSOMA MANSONI INFECTIONS: Clifford L. Spingarn, Morton H. Edelman, Theodore Gold, Harry Yarnis and Robert Turell. New England J. Med. 256:290 (14 Feb.), 1957.

Rectal biopsy was performed on 106 native Puerto Ricans. This method is superior to stool examination for demonstrating the ova. A sigmoidoscope (the reviewer has also used an anoscope to visualize the lowermost rectal valve) is passed, and with a Yarnis bladder punch or a Turell angulated cutting forceps, a small piece of tissue is removed from the central portion of the first or second rectal valves. This procedure is painless, and only slight bleeding results. The fragment is compressed between two slides, which may be held with adhesive, and examined under the low power of the microscope. The fragment placed in saline solution for a short time before being placed on a slide will have increased transparency. Ova were found in 93 per cent by biopsy, and 83 per cent by stool examination. Viable mature ova are relatively large, with characteristic lateral spines. Each contains a fully developed miracidium. Movement of the larva is often observed, and occasionally one may be seen to break out of its shell and move rapidly. Immature viable ova are smaller, containing an undifferentiated embryo, often appearing as a central clear area surrounded by opaque granular material. Degenerated ova contain remnants of their original material, with or without the lateral spine.

After treatment with Fuadin, the number of nonviable ova increases. An abnormal appearance of the rectal mucosa in these patients is the exception rather than the rule.

SAMUEL L. IMMERMAN

DRUG SENSITIVITY TESTS ON ESCHERICHIA COLI STRAINS FROM CASES OF GASTROENTERITIS IN INFANTS, CHILDREN AND ADULTS: A. Banerjea and Gouri Banerjee. Ann. Biochem. & Exper. Med. 16:73 (Feb.), 1956.

Ten different strains of *Escherichia coli* were obtained from 121 cases of gastroenteritis in infants, children and adults, and from 14 normal infants serving as controls. Their sensitivity to various antibiotics and sulfonamides was tested with the filter paper disk method. The same strains were found in patients as well as in normal controls. The sensitivity of these strains was alike in both groups. All were resistant to penicillin and sulfonamides. Dihydrostreptomycin and chloromycetin were the most effective drugs, while tetracyclines were also useful but inhibited bacterial growth somewhat less. There was no specific strain demonstrated causing gastroenteritis and no specific therapeutic agent found.

H. B. EISENSTADT

BOOK REVIEWS FOR GASTROENTEROLOGISTS

CHIRURGIE DER LEBER—KLINIK UND TECHNIK: Priv. Doz. Dr. M. Reifferscheid, Oberartz der Chirurgischen Universitats Klinik, Bonn with a foreword by Prof. Dr. E. Freiherr von Redwitz, Vorm. Direktor der Chirurgischen Universitats Klinik, Bonn. 167 pages, illustrated. Georg Thieme Verlag, Stuttgart, Germany, 1957. Price $8.60.

A well composed, profusely illustrated, beautifully printed and bound book dealing with surgery of the liver.

Surgeons who read German will find a great many newer concepts describing operations on the liver. It is recommended as a valuable asset to the surgeon's library.

AKTUELLE DIABETESFRAGEN—Symposion in Hamburg am 24 Januar 1957: Professor Dr. F. Bertram und Dr. J. Kuntze, den Zweiten Medizinischen Klinik des Allgermeinen Krankenhauses, Hamburg-Barmbek. 80 pages. Georg Thieme Verlag, Stuttgart, Germany, 1957. Price $1.35.

This is a symposium on diabetes with special reference to the oral administration of Sulfonyl (Tolbutamid) in diabetes.

A very interesting observation by H. Stark from the eye clinic of the Allgemeinen Krankenhaus, Hamburg-Barmbek, was that 950 patients with diabetes taking the oral preparation, were observed for six months and in 80 per cent, Stark and his colleagues found changes in refraction, a transitory hyperopia which appeared on the 4th and 5th days of treatment and lasted about 2 to 3 weeks and gradually disappeared. Further observations revealed tendency to bleed. Other observers did not substantiate Stark's findings. They mentioned, however, skin manifestations, liver and kidney irritations.

This is a very interesting and instructive symposium dealing with oral therapy in diabetes.

L'AGOBIOPSIA EPATICA (LIVER BIOPSY): M. Banche and M. Fazio. Preface by Professor G. C. Dogliotti. 201 pages, illustrated. Edizioni Minerva Medica, Torino, Italy, 1957. Price L.2300.

Liver biopsy as a means of diagnosis is excellently written and illustrated. Physicians who employ this method will find it well worth their time to look over this treatise. Although written in Italian, the illustrations are self-explanatory and the various types of needles used and/or their modification are clearly depicted.

Translation into several languages would be advisable.

ANNUAL REVIEW OF MEDICINE: David A. Rytand, Editor, Stanford University School of Medicine, William Creger, Associate Editor, Stanford University School of Medicine. Volume 8. 530 pages. Annual Reviews, Inc., Palo Alto, Calif., 1957. Price $7.00.

In this eighth volume of "Annual Review of Medicine", as in previous volumes, the editors and collaborators attempt to bring to the reader's attention, from the world's medical literature, the new and important investigations and diagnostic procedures of all phases of medicine.

From the 23 topics presented, the reviewer selected several chapters which he recommends of particular interest to all physicians. These chapters are: diseases of the gastrointestinal tract; cardiovascular system (medical and surgical); the kidneys; nutrition and nutritional diseases; nervous system; radioisotopes in medicine; special therapeutics of helminthic diseases; and tolerance to and physical dependence on opiates, barbiturates and alcohol.

An extensive list of literature cited follows each topic, a name and cross index complete the volume.

DIABETES MELLITUS WITH EMPHASIS ON CHILDREN AND YOUNG ADULTS: T. G. Danowski, B.A., M.D., Renziehausen Professor of Research Medicine; Senior Staff Physician at the Children's, Presbyterian-Women's and Elizabeth Steel Magee Hospitals; Consultant in Metabolism, Oakland Veteran's Administration Hospital. 510 pages, illustrated. The Williams & Wilkins Co., Baltimore, Md., 1957. Price $13.50.

The monograph is divided into 26 chapters with extensive references at the end of each chapter.

From the reviewer's viewpoint, Dr. Danowski has covered diabetes, its complications and therapy from all angles. Each reference is represented in the proper place and the extensive table of contents and index makes it easy to locate any desired subject.

The book can be recommended not only to pediatricians, but also to physicians in general.

PHYSICAL EXAMINATION IN HEALTH AND DISEASE: Rudolph H. Kampmeier, A.B., M.D., Professor of Medicine, Vanderbilt University School of Medicine, Visiting Physician, Vanderbilt University Hospital, Chief of the Medical Outpatient Service, Vanderbilt University Hospital, Nashville, Tenn. 774 pages, illustrated. Second Edition. F. A. Davis Company, Philadelphia, Pa., 1957. Price $9.50.

The first volume went through several reprints. This volume undoubtedly will go through reprint after reprint, because of the excellent material which the student and physician will find between the covers.

The aim of the writer is to teach the student to complete the examination of the body as a whole, that is to examine each part systematically including the neurological and other aspects, rather than to have the neurologist and the ophthalmologist complete the examination.

Not only are the common conditions portrayed, but the author has added rarer conditions to amplify the text and thus add to the value of the book.

Dr. Kampmeier insists that a good history must be obtained before physical examination is begun. He states that taking a good history is an art and that thus the student or young physician acquaints himself with the composite picture of a given disease. It is by careful interviews at the bedside that etiologic factors, anatomic changes, physiologic disturbances, functional abnormalities and the natural course of the disease will be learned and understood.

The reader is referred to page 400, where a detailed description of the heart and blood vessels will be found. Many helpful suggestions with schematic and other illustrations will aid in arriving at a diagnosis. This chapter is spread over 116 pages including references. On pages 517 to 578, the normal abdomen and its variations with illustrations will intrigue the reader. Page 630, the musculoskeletal system and extremities are enlightening and worthwhile reading.

All in all, the reviewer finds "Physical Examination in Health and Disease" a well written, illustrated and more than well printed bound volume. He recommends it to medical students and physicians as a valuable aid in diagnosis.

THE MALABSORPTION SYNDROME: David Adlersberg, M.D., Associate Attending Physician for Metabolic Diseases, The Mt. Sinai Hospital, New York, N. Y., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y., with contributors to the Symposium by Members of the Staff of The Mt. Sinai Hospital, New York, N. Y. Guest Contributors: W. Trevor Cooke, Margot Shiver. Foreword: Henry L. Bockus. 252 pages, illustrated. Grune & Stratton, New York, N. Y., 1957. Price $5.50.

A very interesting study dealing with the Malabsorption Syndrome by a group of physicians working in a well equipped hospital and laboratory, gives the medical profession an insight into the possible causes and secondary involvement of organs remote from the gastrointestinal tract.

Unfortunately, the busy general practi-

tioner, unless inquisitive, may glance through the monograph and find that it is beyond his grasp. The reviewer, however, found it more than interesting and has added a great deal to his knowledge regarding malabsorption.

Dr. Adlersberg, his co-workers and publisher are to be congratulated in bringing out this original and useful volume, which undoubtedly will find its place in medical literature.

GOEPP'S MEDICAL STATE BOARD QUESTIONS AND ANSWERS: Harrison F. Phippin, M.D., Professor of Clinical Microbiology, Graduate School of Medicine, University of Pennsylvania. Editorial Consultants: William S. Blakemore, M.D., Jefferson H. Clark, M.D., George M. Eisenberg, D.Sc., George L. Hoffman, M.D. Ninth Edition. 569 pages. W. B. Saunders Company, Philadelphia, Pa., 1957. Price $8.00.

Many of us have used Goepp's Medical State Board Questions in preparing for licensing examinations. As medicine has advanced, so has Goepp's questions and answers advanced. New methods of diagnosis and drugs were added with each revision of the book. This ninth edition is one of the most up to the minute books on the whole field of medicine, including surgery, neurology and other medical and surgical specialties.

It is recommended to all medical students and physicians as an excellent and handy reference volume.

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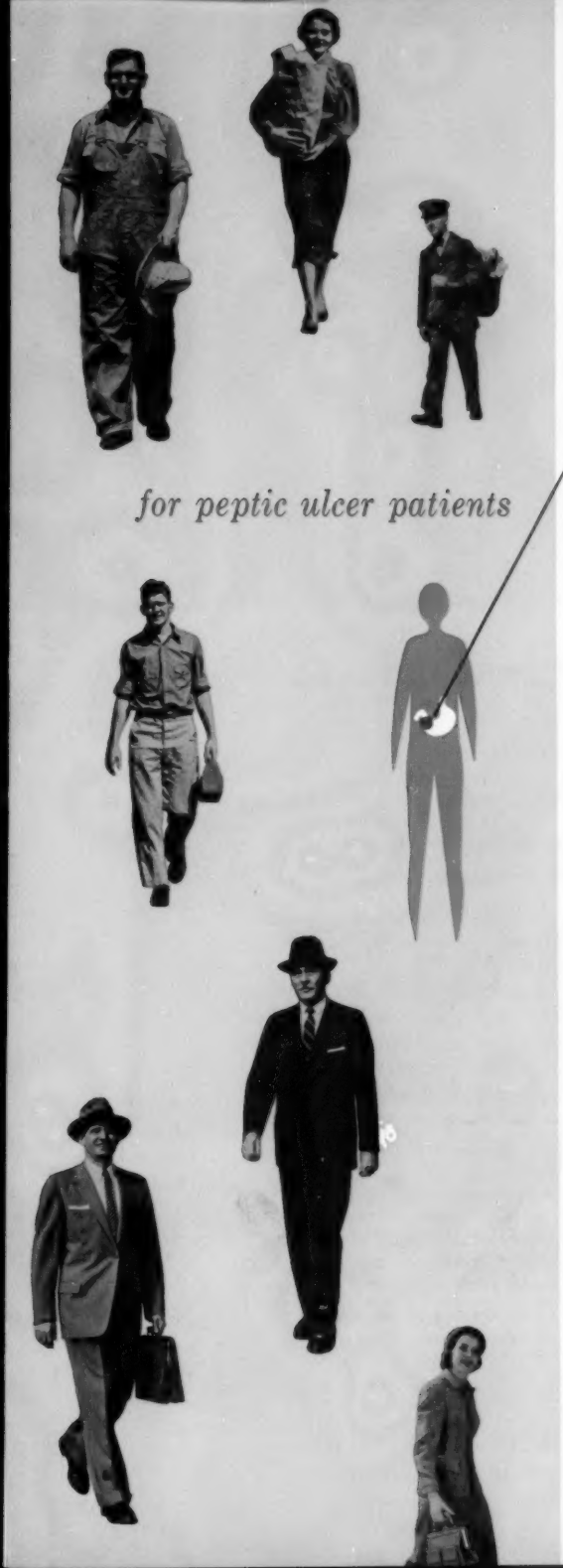

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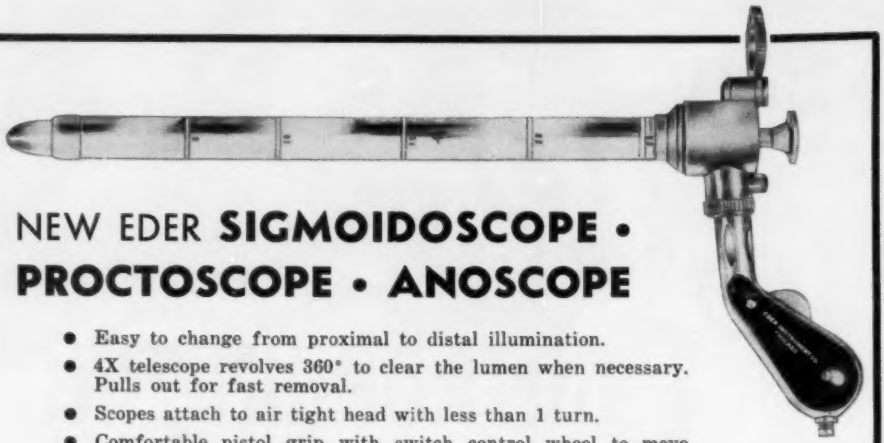

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[1] *American Journal of Gastroenterology* 28:439, 1957.

[2] *British Medical Journal* 2:827, 1955.

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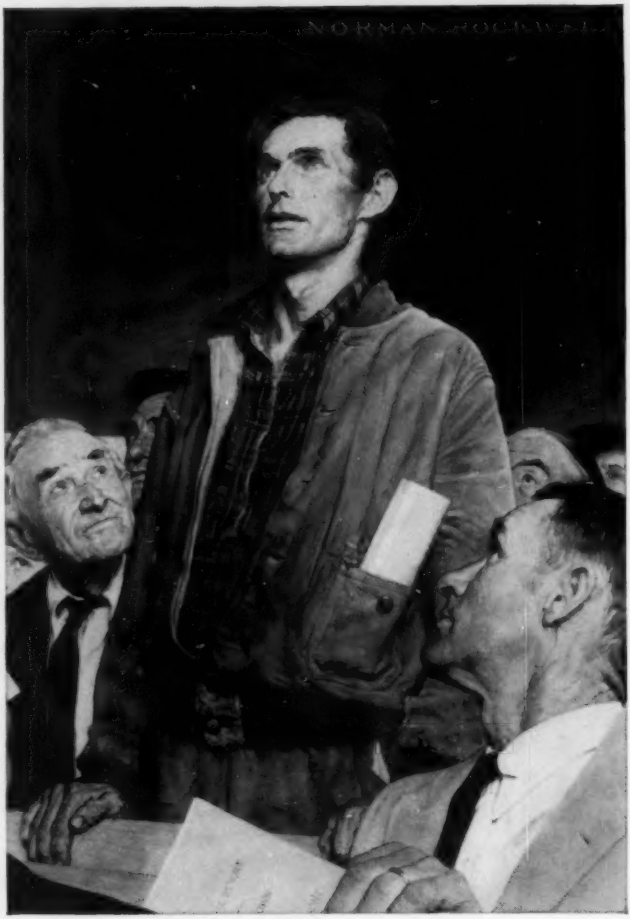

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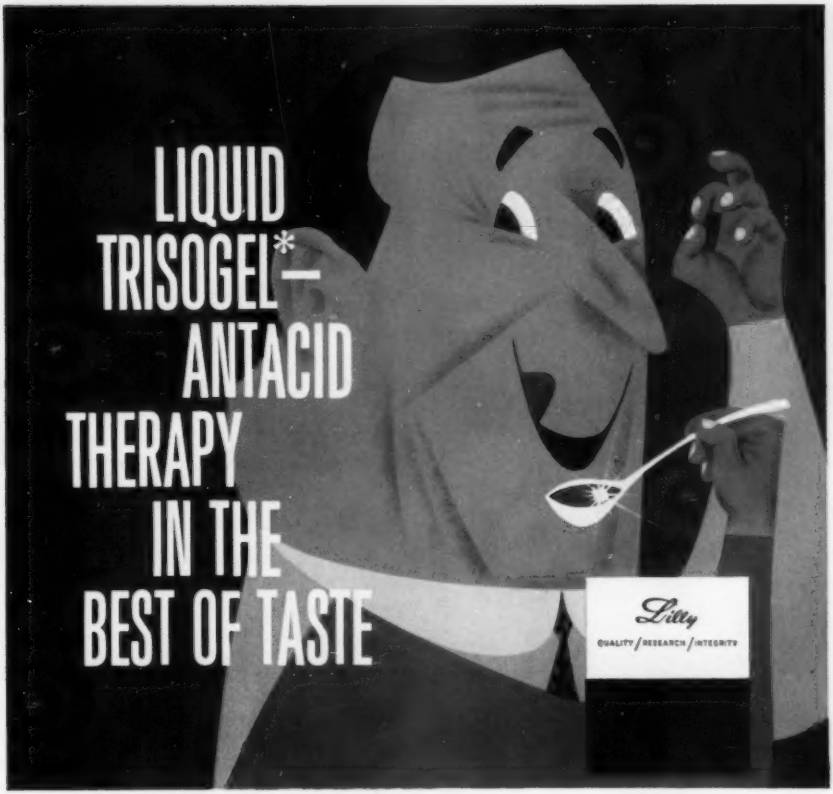

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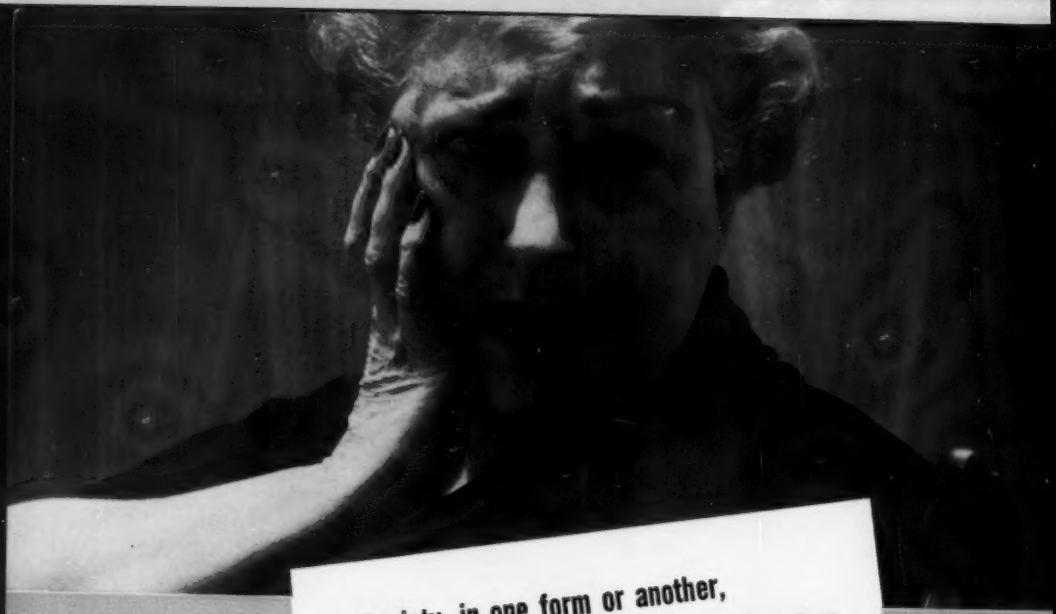

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1. Hollister, L.H., et al.: Dis. Nerv. System 17:289 (Sept.) 1956.

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